INESSS
LE SAVOIR PREND FORME

FINAL REPORT

Reevaluation of eligibility criteria for palivizumab (Synagis®) for the prevention of severe syncytial respiratory virus infections in children

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RÉSUMÉ

Le 2 juin 2015, l'Institut national d'excellence en santé et en services sociaux (INESSS) a reçu une demande de la Direction générale des services de santé et de médicine universitaire (DGSSMU) du ministère de la Santé et des Services sociaux (MSSS) visant à réévaluer les critères d'admissibilité au programme québécois d'immunoprophylaxie par le palivizumab (Synagis[MC]) pour la prévention de l'infection par le virus respiratoire syncytial (VRS) chez l'enfant, en vue d'une optimisation de l'usage du palivizumab durant la saison 2015-2016.

Le cadre d'évaluation retenu aux fins de la réalisation du mandat est inspiré de celui établi pour l'évaluation des médicaments aux fins d'inscription sur les listes des médicaments assurés au Québec. En effet, il inclut les volets de la valeur thérapeutique, de la justesse du prix, du rapport entre le coût et l'efficacité du produit, des conséquences sur la santé de la population et sur les autres composantes du système de santé et des services sociaux et celui des autres considérations notamment de nature éthique ou sociétale.

Travaux d'évaluation (saison 2015-2016)

Dans les délais impartis, l'INESSS a été en mesure, entre autres, de procéder à une recension ciblée de la documentation scientifique, de prendre connaissance des recommandations des sociétés canadienne et américaine de pédiatrie, d'échanger avec le fabricant du produit (AbbVie) et de consulter un comité d'experts. Le rôle des membres du comité était de collaborer à l'analyse des données scientifiques et de fournir l'expertise clinique dans le domaine de l'immunoprophylaxie par le palivizumab chez les enfants à risque d'infection grave par le VRS. Le comité regroupait notamment des infectiologues, des pneumologues et des cardiologues spécialisés en pédiatrie, des pédiatres, des néonatalogistes ainsi que des membres du Comité scientifique d'évaluation des médicaments aux fins d'inscription (CSEMI). Une attention particulière a été portée à la composition de ce comité, afin que ses membres soient issus des principaux réseaux universitaires intégrés de santé (RUIS), où sont soignées les clientèles pédiatriques vulnérables visées par l'immunoprophylaxie à l'étude dans le présent rapport. Parmi les membres, figuraient ceux qui ont reçu d'Héma-Québec le mandat d'évaluer les demandes d'autorisation hors critères relatives au palivizumab. En dépit des étapes réalisées, l'INESSS jugeait que son analyse n'était pas suffisamment approfondie pour respecter ses standards de qualité et de rigueur scientifique. Une approche inspirée par la prudence en a ainsi découlé, menant au dépôt d'un rapport de propositions préliminaires (non publié), accompagné d'une recommandation à poursuivre les travaux scientifiques en vue de la saison 2016-2017. De fait, une analyse scientifique rigoureuse et exhaustive des données cliniques s'imposait.

Précisons que des modifications aux critères d'utilisation du palivizumab en vue de la saison 2015-2016 ont tout de même été apportées à la circulaire d'Héma-Québec à partir, notamment, de certaines propositions préliminaires du comité consultatif incluses dans le rapport préliminaire et des recommandations des sociétés canadienne et américaine de pédiatrie.

Travaux d'évaluation (saison 2016-2017)

Une revue systématique de la documentation scientifique a été menée par l'INESSS [2016, voir l'annexe I], afin de répertorier toute l'information pertinente relative à la question suivante : « Quelle est l'efficacité du palivizumab en prophylaxie pour réduire le risque de complications associées au VRS (hospitalisations, séquelles à long terme et décès) chez les enfants, comparativement à l'administration d'un placébo ou à l'absence de prophylaxie? ». Les résultats extraits des études incluaient, outre les

hospitalisations, les séjours dans une unité de soins intensifs et le recours à l'assistance respiratoire. La recherche a porté sur plusieurs populations d'enfants qui présentent des facteurs de risque reconnus d'infection grave ou un problème de santé suspecté d'en être un.

En parallèle de la revue systématique, l'INESSS a procédé au recensement et à l'analyse de plusieurs études observationnelles de cohortes, prospectives ou rétrospectives, qui se rapportaient principalement soit aux conséquences de l'usage du palivizumab dans un contexte de vie réelle dans différents pays, soit à la détection de groupes d'enfants qui présentaient des facteurs de risque associés à une incidence accrue d'hospitalisations dues à une infection par le VRS.

Par ailleurs, l'INESSS a consulté à nouveau le comité consultatif auquel s'est jointe une pédiatre spécialisée dans les soins de santé dans le Grand Nord québécois, soit les régions sociosanitaires du Nord-du-Québec, du Nunavik et des Terres-Cries-de-la-Baie-James.

Les principaux constats découlant de l'ensemble des étapes réalisées sont les suivants :

- La revue systématique a permis de confirmer l'absence d'études sur plusieurs des populations ciblées et l'existence d'un très faible nombre d'études comparatives, à répartition aléatoire de qualité, dont la validité externe est amoindrie par les progrès en matière de soins de santé en pédiatrie réalisés au cours des dernières décennies. La documentation répertoriée en parallèle était constituée principalement d'études observationnelles prospectives ou rétrospectives dont la qualité était très variable, soit de très faible à bonne. L'INESSS a constaté à un problème majeur d'hétérogénéité des différentes études, ce qui a rendu la comparaison des résultats très ardue et leur application à notre contexte clinique, limitée. Les sources les plus fréquentes d'hétérogénéité influant sur les résultats sont, notamment, la variation des caractéristiques des saisons du VRS selon les régions, la non-uniformité des normes de pratique selon les centres participants et leur évolution dans le temps ainsi que l'absence de groupe témoin. Un autre des problèmes rencontrés est le manque de puissance statistique de certaines études qui portaient sur de petits nombres d'enfants, entre autres, ceux atteints d'une maladie à faible prévalence. Enfin, il est peu probable que des études de qualité supérieure soient éventuellement réalisées, particulièrement dans le cas des problèmes de santé rares.

- L'abrogation du critère oncernant les bébés prématurés nés entre 33 et 35 6/7 semaines de grossesse ne semble pas, à première vue, avoir eu de conséquences cliniques significatives chez cette population par rapport à la population pédiatrique globale, et ce, ni sur le nombre d'hospitalisations, ni sur la gravité de l'atteinte durant la saison du VRS 2015-2016. Cependant, il demeure impératif d'évaluer les conséquences du retrait de ce critère sur plusieurs années, parce que les caractéristiques des saisons du VRS varient dans le temps. D'ailleurs la saison dernière a présenté une dynamique particulière, soit un début tardif de la période d'infection et une prévalence importante du virus de l'influenza de type B.

- La consultation d'une experte des soins de santé dispensés dans le Grand Nord québécois a permis de mieux comprendre le contexte particulier de cette région et de déterminer les besoins de santé qui n'y sont pas comblés. Ainsi, il s'avère que les jeunes bébés du Nunavik nés à terme, qui ne présentent aucun facteur médical de risque d'infection grave pouvant conduire à une hospitalisation, sont tout de même très à risque de développer des complications qui peuvent requérir un transfert en centre hospitalier universitaire en région urbaine. Les modalités de transport aérien sont complexes et difficiles, particulièrement à partir des villages les plus éloignés,

et peuvent comporter des risques pour l'enfant en raison des délais d'attente d'avoir accès à des soins spécialisés. Les bébés prématurés de cette région dont l'âge gestationnel (AG) est inférieur à 36 semaines représentent également une population à cibler. Enfin, l'organisation des soins dans le Grand Nord québécois ne semble pas une entrave à la réussite d'un programme d'immunoprophylaxie adapté à cette région.

- En dépit de l'élaboration d'un modèle pharmacoéconomique adapté au Québec, il s'avère qu'aucune conclusion fiable n'a pu être tirée au regard de l'efficience du palivizumab en prophylaxie dans les différentes populations visées dans les recommandations du présent rapport. Cela s'explique par la faiblesse de la preuve clinique concernant certaines d'entre elles ou par l'absence totale de données sur d'autres. Par conséquent, l'efficience du palivizumab n'a pas pu être évaluée.

- Par ailleurs, les coûts pour le palivizumab ont été relativement stables au fil des saisons 2010-2011 à 2014-2015 ; ils augmentaient en moyenne au rythme de 1,8 % annuellement. Ces coûts sont passés de 16,8 M$ en 2014-2015 à 8,9 M$ en 2015-2016, soit une diminution de 47 %. Le nombre d'enfants traités a diminué de 35 %, alors que le coût moyen par enfant a diminué de 18 %. Pendant ce temps, dans le reste du Canada, le nombre d'enfants traités a aussi diminué, mais seulement de 9,6 %. Précisons que le nombre d'autorisations hors critères a également diminué en 2015-2016.

- La vulnérabilité des populations concernées, l'anxiété associée à l'hospitalisation d'enfants qui ont été parfois hospitalisés pendant une période prolongée à la naissance et, enfin, les risques et les inconvénients des hospitalisations pour l'enfant et sa famille sont des éléments importants à considérer.

L'évaluation du palivizumab en immunoprophylaxie à l'aide du cadre d'évaluation retenu a présenté des défis. Il s'agit d'un produit à visée préventive, plutôt que curative, des méfaits d'une infection par le VRS susceptibles de se compliquer. La valeur thérapeutique du produit a d'abord été étudiée relativement aux différentes populations jugées à risque. Il s'avère que la qualité de la preuve disponible (données cliniques et épidémiologiques) concernant plusieurs de ces populations est généralement faible, voire inexistante. C'est pourquoi l'opinion des experts et des sociétés canadienne et américaine de pédiatrie a dû être prise en compte, de telle sorte que la valeur thérapeutique a pu être établie sur une appréciation clinique que l'INESSS considère tout à fait acceptable compte tenu de la nature du médicament. Dans cette optique, il était d'une importance capitale de former un comité qui assure une bonne représentativité. Soulignons que les considérations économiques n'ont pas été prises en compte dans l'appréciation de la valeur thérapeutique. À partir du moment où la pertinence scientifique ou clinique de l'usage du palivizumab a été établie, l'INESSS a ensuite évalué l'ensemble des considérations propres à la réduction des méfaits associés à une infection par le VRS, laquelle peut se compliquer au point de nécessiter l'hospitalisation de l'enfant qui en est atteint. L'approche globale préconisée constitue, de l'avis de l'INESSS, le meilleur niveau de preuve qui puisse appuyer les recommandations formulées dans le présent rapport.

Les tableaux suivants synthétisent les recommandations de l'INESSS relatives à l'usage du palivizumab en vue de la saison du VRS 2016-2017 chez les différentes populations et à ses modalités d'administration.

Bébés prématurés sans autre facteur de risque que la prématurité

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	**Critère n°1** Les bébés nés à moins de 33 semaines de grossesse et âgés de moins de 6 mois au début de la saison du VRS.
Saison 2015-2016	**Critère n°1** Les bébés nés à moins de 33 semaines de grossesse et âgés de moins de 6 mois au début de la saison du VRS.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Sans être indispensable, chez les bébés prématurés, sans dysplasie bronchopulmonaire, seulement s'ils sont nés avant la 30e semaine de gestation et âgés de moins de 6 mois au début de la saison du VRS.
AAP, 2014	Chez les bébés prématurés, seulement si leur AG est inférieur à 29 semaines et s'ils sont âgés de moins de 12 mois au début de la saison du VRS.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Notario *et al.*, 2014; Andabaka *et al.*, 2013; Tavsu *et al.*, 2013; Checchia *et al.*, 2011; Grimaldi *et al.*, 2007; IMpact-RSV, 1998.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de maintenir le critère de 2015-2016.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien du critère de 2015-2016 : Les bébés nés à moins de 33 semaines de grossesse et âgés de moins de 6 mois au début de la saison du VRS**

Bébés prématurés présentant des facteurs de risque mis en évidence par Sampalis [2008]

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	**Critère n°2** Les bébés nés entre 33 et 35 6/7 semaines de grossesse, âgés de moins de 6 mois au début de la saison des infections par le VRS et qui présentent un pointage de plus de 48 à l'échelle de risque, tirée de Sampalis [2008].
Saison 2015-2016	Abrogation du critère
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	La prophylaxie par le palivizumab n'est pas recommandée
AAP, 2014	
DOCUMENTATION SCIENTIFIQUE RETENUE	
Anderson *et al.*, 2016; analyse regroupée d'Anderson (manuscrit en cours de révision par les pairs); Ryan *et al.*, 2016; Stranak *et al.*, 2016; Ambrose *et al.*, 2014 (REPORT); Notario *et al.*, 2014; Blanken *et al.*, 2013; Mitchell *et al.*, 2011 (CARESS); Paes *et al.*, 2009, Mitchell *et al.*, 2006; Law *et al.*, 2004; Wegner *et al.*, 2004; IMpact-RSV, 1998.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont majoritairement d'avis de maintenir l'abrogation du critère de 2014-2015, conditionnellement à la mise en place d'un processus objectif et indépendant de suivi de cette population.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien de l'abrogation du critère de 2014-2015, conditionnellement à l'instauration d'un suivi structuré et indépendant de l'état des enfants visés**

Enfants atteints de dysplasie bronchopulmonaire ou d'une maladie pulmonaire chronique du nouveau-né

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	**Critère n° 3** Les enfants âgés de moins de 24 mois, présentant : • une maladie chronique pulmonaire; ou • une condition médicale avec complications respiratoires sévères; **et** • qui ont eu besoin d'oxygène dans les 6 mois qui précèdent la saison du VRS; ou • qui en besoin pendant la saison du VRS.
Saison 2015-2016	**Critère n° 2** Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, atteints d'une maladie pulmonaire chronique du nouveau-né (définie par le besoin d'oxygène à 36 semaines d'âge gestationnel) ou de dysplasie bronchopulmonaire (définie par un besoin d'oxygène à 28 jours de vie et jusqu'à au moins 36 semaines d'âge gestationnel) **et** : • qui ont eu besoin d'oxygène dans les 6 mois qui précèdent la saison du VRS; ou • qui en ont besoin pendant la saison du VRS.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Durant la première année de vie des enfants âgés de moins de 12 mois au début de la saison du VRS, atteints d'une maladie pulmonaire chronique de la prématurité (définie comme un besoin d'oxygène à 36 semaines d'AG) et qui ont un besoin constant de diurétiques, de bronchodilatateurs, de stéroïdes ou de suppléments d'oxygène. Durant la seconde année de vie des enfants âgés de 12 mois à moins de 24 mois avant le début de la saison du VRS, atteints d'une maladie pulmonaire chronique de la prématurité (définie comme un besoin d'oxygène à 36 semaines d'AG), qui reçoivent toujours de l'oxygène ou qui en ont été sevrés au cours des trois mois précédant la saison du VRS en cours.
AAP, 2014	Durant la première année de vie des bébés prématurés qui ont développé une maladie pulmonaire chronique liée à la prématurité, définie par le besoin d'oxygène à une concentration supérieure à 21 % durant les 28 premiers jours de vie à un AG inférieur à 32 semaines 0 jour. Durant la seconde année de vie des enfants satisfaisant à la définition de la maladie pulmonaire chronique liée à la prématurité ci-dessus et qui continuent d'avoir besoin d'un traitement (corticothérapie chronique, diurétique, oxygène) au cours des six mois précédant le début de la seconde saison du VRS.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Notario *et al.*, 2014; Mitchell *et al.*, 2011 (CARESS); Chang *et al.*, 2010; Mitchell *et al.*, 2006; Grimaldi *et al.*, 2004; Pedraz *et al.*, 2003; Boyce *et al.*, 2000; IMpact-RSV 1998.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de modifier le critère de 2015-2016 pour en faciliter la compréhension.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Modification du critère de 2015-2016 :** - **Les bébés nés à terme ou près du terme, âgés de moins de 24 mois au début de la saison du VRS, atteints d'une maladie pulmonaire chronique du nouveau-né, définie par un besoin d'oxygénothérapie à la naissance qui a persisté en raison d'une atteinte pulmonaire chronique autre que celles désignées dans les autres critères;** **ou**

	- **Les bébés prématurés, âgés de moins de 24 mois au début de la saison du VRS, atteints de dysplasie bronchopulmonaire, définie par un besoin d'oxygénothérapie peu après la naissance et qui persiste jusqu'à au moins 28 jours de vie et jusqu'à un âge gestationnel d'au moins 36 semaines, et ce, en présence d'antécédents caractéristiques de la maladie;** **et** - **qui ont eu un besoin d'oxygénothérapie persistant dans les 6 mois précédant le début de la saison du VRS ou qui en ont besoin durant la saison du VRS.**

Enfants atteints de fibrose kystique

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	**Critère n^{o} 3** Les enfants âgés de moins de 24 mois, présentant : • une maladie chronique pulmonaire; ou • une condition médicale avec complications respiratoires sévères; **et** • qui ont eu besoin d'oxygène dans les 6 mois qui précèdent la saison du VRS; ou • qui en besoin pendant la saison du VRS. Certains cas autorisés à la suite d'une demande hors critères
Saison 2015-2016	**Critère n^{o} 3** Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, atteints de fibrose kystique et qui présentent des symptômes respiratoires ou un retard staturo-pondéral significatifs.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Le palivizumab ne devrait pas être administré de façon routinière aux enfants atteints de fibrose kystique. Il peut cependant être envisagé dans les cas suivants : Enfants âgés de moins de 24 mois atteints de fibrose kystique, seulement s'ils reçoivent de l'oxygène à domicile, s'ils ont été hospitalisés de façon prolongée en raison de la maladie pulmonaire grave ou s'ils sont gravement immunodéprimés.
AAP, 2014	Le palivizumab ne devrait pas être administré de façon routinière chez les enfants atteints de fibrose kystique. Il peut cependant être envisagé dans les circonstances suivantes : Durant la première année de vie d'un enfant atteint de fibrose kystique avec une évidence clinique de maladie chronique pulmonaire ou d'un retard staturo-pondéral. Durant la deuxième année de vie d'un enfant atteint de fibrose kystique qui a reçu le palivizumab durant sa première année, s'il présente des signes attestant d'une condition médicale grave (hospitalisation pour une exacerbation pulmonaire durant la première année ou anomalies persistantes à la radiographie ou la tomographie du thorax malgré une stabilité de la maladie) ou s'il présente un retard staturo-pondéral (≤ 10^{e} percentile).
DOCUMENTATION SCIENTIFIQUE RETENUE	
Groves *et al.*, 2016; Robinson *et al.*, 2014; Winterstein *et al.*, 2013; Giebels *et al.*, 2008.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de maintenir le critère de 2015-2016.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien du critère de 2015-2016 : Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, atteints de fibrose kystique et qui présentent des symptômes respiratoires ou un retard staturo-pondéral significatifs.**

Enfants présentant des troubles neuromusculaires

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucun critère; certains cas autorisés à la suite d'une demande hors critères
Saison 2015-2016	**Critère n° 4** Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, dont l'évacuation des sécrétions des voies aériennes est entravée de façon important en raison d'un trouble neuromusculaire.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Le palivizumab ne devrait pas être administré de façon routinière aux enfants présentant une obstruction des voies aériennes supérieures. Toutefois, ce médicament peut être considéré pour les enfants âgés de moins de 24 mois qui reçoivent de l'oxygène à domicile, ont eu une hospitalisation prolongée causée par une maladie pulmonaire grave ou qui sont gravement immunodéprimés.
AAP, 2014	Le palivizumab pourrait être administré au cours de la première année de vie des enfants présentant une maladie neuromusculaire dont les manifestations diminuent la capacité d'évacuation des sécrétions des voies aériennes supérieures en raison d'une toux inefficace, car il est connu qu'ils sont à risque d'hospitalisation prolongée en cas d'infection des voies respiratoires inférieures graves.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Kristensen *et al.*, 2012; Zachariah *et al.*, 2011.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de maintenir le critère de 2015-2016.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien du critère de 2015-2016 : Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, dont l'évacuation des sécrétions des voies aériennes est entravée de façon important en raison d'un trouble neuromusculaire. Le diagnostic doit être fourni sur la demande**

Enfants présentant des anomalies congénitales des voies respiratoires supérieures

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucun critère; certains cas autorisés à la suite d'une demande hors critères
Saison 2015-2016	**Critère n° 5** Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS dont l'évacuation des sécrétions des voies aériennes est entravée de façon importante, en raison d'anomalies congénitales des voies aériennes supérieures.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Le palivizumab ne devrait pas être administré de façon routinière aux enfants présentant une obstruction des voies aériennes supérieures. Toutefois, ce médicament peut être considéré pour les enfants âgés de moins de 24 mois qui reçoivent de l'oxygène à domicile, ont eu une hospitalisation prolongée causée par une maladie pulmonaire grave ou qui sont gravement immunodéprimés.
AAP, 2014	Le palivizumab pourrait être administré durant la première année de vie des enfants présentant une anomalie congénitale qui diminue la capacité d'évacuation des sécrétions des voies aériennes supérieures en raison d'une toux inefficace, car il est connu qu'ils sont à risque d'hospitalisation prolongée en cas d'infection des voies respiratoires inférieures graves.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Kristensen *et al.*, 2012; Zachariah *et al.*, 2011.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de maintenir le critère de 2015-2016.	

RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien du critère de 2015-2016 : Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS dont l'évacuation des sécrétions des voies aériennes est entravée de façon importante, en raison d'anomalie congénitale des voies aériennes supérieures. Le diagnostic doit être fourni sur la demande.**

Enfants atteints de maladies cardiaques

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	**Critère n°4** Les enfants âgés de moins de 24 mois souffrant de cardiopathie congénitale qui entraîne des conséquences hémodynamiques cliniquement significatives.
Saison 2015-2016	**Critère n°6** Les enfants âgés de moins de 12 mois au moment du début de la saison du VRS, atteints de cardiopathie congénitale, de cardiomyopathie ou de myocardite qui entraînent des conséquences hémodynamiques cliniquement significatives ou souffrant d'hypertension artérielle pulmonaire modérée ou grave (la demande doit être soumise par un cardiologue pédiatrique pour garantir la justesse du diagnostic).
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Chez les enfants âgés de moins de 12 mois au moment du début de la saison du VRS atteints d'une cardiopathie congénitale entraînant des conséquences hémodynamiquement significative.
AAP, 2014	Chez les enfants âgés de moins de 12 mois au moment du début de la saison du VRS atteints d'une cardiopathie congénitale entraînant des conséquences hémodynamiquement significative, incluant : • Enfants atteints d'une maladie cardiaque acyanogène qui reçoivent un médicament pour contrôler l'insuffisance cardiaque congestive et qui nécessitera une chirurgie cardiaque. • Enfants souffrant d'hypertension artérielle pulmonaire modérée à grave.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Harris *et al.*, 2011; Bellavance *et al.*, 2006; Feltes *et al.*, 2003; Boyce *et al.*, 2000; Wang *et al.*, 1997.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de maintenir le critère de 2015-2016.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien du critère de 2015-2016 : Les enfants âgés de moins de 12 mois, au moment du début de la saison du VRS, atteints de cardiopathie congénitale, de cardiomyopathie ou de myocardite qui entraîne des conséquences hémodynamiques cliniquement significatives ou souffrant d'hypertension artérielle pulmonaire modérée ou grave (la demande doit être soumise par un cardiologue pédiatrique pour garantir la justesse du diagnostic).**

Enfants immunodéprimés

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	**Critère n° 5** Enfants âgés de moins de 24 mois ayant subi une greffe de moelle osseuse ou une greffe de cellules souches dans les 6 mois qui précèdent la saison du VRS ou pendant la saison du VRS. Certains cas autorisés à la suite d'une demande hors critères.
Saison 2015-2016	**Critère n° 7** Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, ayant subi une greffe de moelle osseuse, de cellules souches ou d'organe solide (cœur, foie

	ou poumon), dans les 6 mois qui précèdent la saison du VRS ou pendant la saison du VRS.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Le palivizumab ne devrait pas être administré de façon routinière aux enfants atteints de déficits immunitaires, sauf à ceux âgés de moins de 24 mois qui reçoivent de l'oxygène à domicile, ont eu une hospitalisation prolongée causée par une maladie pulmonaire grave ou qui sont gravement immunodéprimés.
AAP, 2014	Le palivizumab pourrait être administré aux enfants âgés de moins de 24 mois qui, durant la saison du VRS, sont gravement immunodéprimés ou qui subiront une greffe de cœur.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Asner *et al.*, 2013; El Saleeby *et al.*, 2008; Hall *et al.*, 1986.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de maintenir le critère de 2015-2016.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien du critère de 2015-2016 : Les enfants âgés de moins de 24 mois au moment du début de la saison du VRS, ayant subi une greffe de moelle osseuse, de cellules souches ou d'organe solide (cœur, foie ou poumon) dans les 6 mois qui précèdent la saison du VRS ou pendant la saison du VRS.**

Enfants résidant dans les communautés éloignées

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucun critère; certains cas autorisés à la suite d'une demande hors critères
Saison 2015-2016	Aucun critère; certains cas autorisés à la suite d'une demande hors critères
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Le palivizumab devrait être offert aux nourrissons, nés avant la 36e semaine de gestation et âgés de moins de 6 mois au début de la saison du VRS, résidant dans des communautés éloignées où un transport aérien serait requis pour leur hospitalisation. Il est incertain si cette recommandation ne devrait être applicable qu'aux nourrissons inuits, à tous les nourrissons autochtones ou à tous les nourrissons des communautés éloignées.
AAP, 2014	L'usage du palivizumab pour les autochtones résidant en Alaska, ni pour les populations amérindiennes demeurant sur le territoire étatsunien n'est pas formellement recommandé. Cependant, le fardeau lié aux infections graves dues au VRS et les coûts associés au transport aérien requis pour l'hospitalisation des enfants qui en souffrent et qui résident dans des communautés éloignées pourraient justifier un usage élargi pour ces populations.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Banerji *et al.*, 2014; Banerji *et al.*, 2013; Singleton *et al.*, 2003.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis d'ajouter des critères pour les enfants nés à 36 semaines de grossesse ou moins et âgés de moins de 6 mois au début de la saison du VRS, résidant en région éloignée où l'accès à des soins de santé en cas d'état grave requiert un transport aérien, ainsi que pour ceux nés à terme âgés de moins de 3 mois au début de la saison du VRS, résidant en région éloignée où l'accès à des soins de santé en cas d'état grave requiert un transport aérien.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Ajout de critères :** - **Les enfants nés à 36 semaines de gestation ou moins et âgés de moins de 6 mois au début de la saison du VRS ou nés pendant celle-ci, résidant au Nunavik** - **Les enfants nés à terme âgés de moins de 3 mois au début de la saison du VRS**

	ou nés pendant celle-ci, résidant au Nunavik

Enfants atteints du syndrome de Down

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucun critère; certains cas autorisés à la suite d'une demande hors critères
Saison 2015-2016	Aucun critère; aucun cas connu autorisé à la suite d'une demande hors critères
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Le palivizumab ne devrait pas être administré de façon routinière aux enfants atteints du syndrome de Down. Il peut être raisonnable de le faire pour ceux qui sont âgés de moins de 24 mois au début de la saison du VRS et qui reçoivent de l'oxygène à domicile ou ont eu une hospitalisation prolongée causée par une maladie pulmonaire grave ou encore s'ils sont gravement immunodéprimés.
AAP, 2014	Enfants atteints du syndrome de Down s'ils présentent une maladie cardiaque, une maladie pulmonaire chronique, une difficulté à libérer les sécrétions des voies aériennes ou s'ils sont prématurés à moins de 29 semaines d'AG.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Yi *et al.*, 2014.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de ne pas ajouter de critère relativement à cette population.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien de l'absence de critère**

Enfants atteints d'une maladie métabolique

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucun critère; certains cas autorisés à la suite d'une demande hors critères.
Saison 2015-2016	Aucun critère; aucun cas connu autorisé hors critères
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Aucune recommandation formulée concernant cette population.
AAP, 2014	
DOCUMENTATION SCIENTIFIQUE RETENUE	
Kristensen *et al.*, 2012.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de ne pas ajouter de critère et de maintenir le processus d'autorisation hors critères au cas par cas, sous réserve de la révision de la liste des maladies comportant les risques les plus élevés de décompensation importante.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien de l'absence de critère**

Enfants issus d'une naissance multiple

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucun critère; certains cas autorisés à la suite d'une demande hors critères
Saison 2015-2016	Aucun critère; aucun cas connu autorisé à la suite d'une demande hors critères
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Aucune recommandation formulée concernant cette population
AAP, 2014	

DOCUMENTATION SCIENTIFIQUE RETENUE	
Aucune	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de ne pas ajouter de critère et de cesser d'autoriser l'administration de palivizumab aux jumeaux sains d'enfants admissibles à recevoir le palivizumab par le processus d'autorisation hors critères.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien de l'absence de critère**

Enfants âgés de 24 mois ou plus

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucun critère; cas refusés à la suite d'une demande hors critères
Saison 2015-2016	Aucun critère; cas refusés à la suite d'une demande hors critères
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	L'administration du palivizumab à des enfants âgés de 24 mois ou plus au début de la saison du VRS n'est pas recommandée.
AAP, 2014	
DOCUMENTATION SCIENTIFIQUE RETENUE	
Aucune	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de ne pas autoriser l'usage du palivizumab chez cette population.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien de l'absence de critère** **Ajout d'une mention d'exclusion dans la circulaire**

Poursuite de l'administration du palivizumab après la survenue d'une infection par le VRS

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucune mention dans la circulaire
Saison 2015-2016	La prophylaxie devra être cessée dans le cas où une infection à VRS a été confirmée chez l'enfant.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	La poursuite du palivizumab après la survenue d'une infection par le VRS confirmée n'est pas recommandée.
AAP, 2014	
DOCUMENTATION SCIENTIFIQUE RETENUE	
Aucune	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis de ne pas poursuivre l'usage du palivizumab après la survenue d'une infection par le VRS confirmée chez les enfants dont l'état a nécessité une hospitalisation.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Maintien de la mention dans la circulaire avec modification : La prophylaxie par le palivizumab doit être cessée après qu'un enfant ait été hospitalisé en raison d'une infection des voies respiratoires par le VRS dont la présence a été confirmée par un test de dépistage.**

Administration du palivizumab au cours de l'hospitalisation

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	Aucune mention dans la circulaire
Saison 2015-2016	Aucune mention dans la circulaire
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Amorcer l'administration du palivizumab juste avant le congé de l'hôpital. Le palivizumab n'est pas recommandé pour la prévention des infections nosocomiales.
AAP, 2014	Amorcer l'administration du palivizumab juste avant le congé de l'hôpital ou très peu de temps après le départ.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Aucune	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB	
Les membres sont unanimement d'avis que l'administration du palivizumab devrait avoir lieu dans les 48 à 72 heures avant le congé de l'enfant qui y est admissible et que la date de la deuxième dose devrait alors être immédiatement être fixée.	
RECOMMANDATION DE L'INESSS	
Saison 2016-2017	**Ajout de deux mentions dans la circulaire :** - **L'administration du palivizumab devrait avoir lieu dans les 48 à 72 heures avant qu'un enfant admissible au palivizumab obtienne son congé de l'hôpital après la naissance.** - **L'administration du palivizumab en vue de prévenir les infections nosocomiales par le VRS n'est pas indiquée.**

Modalités d'administration du palivizumab

CRITÈRES D'ADMISSIBILITÉ QUÉBÉCOIS	
Saison 2014-2015	L'immunisation par le palivizumab est recommandée selon une administration aux 4 semaines, débutant en novembre. Normalement 5 doses doivent être administrées par saison, avec un maximum de 6 doses, si nécessaire.
Saison 2015-2016	L'immunisation par le palivizumab est recommandée selon une administration aux 4 semaines, débutant à la mi-novembre. Un maximum de 5 doses doit être administré par saison, la dernière dose ne devant pas être administrée au-delà du mois de mars.
RECOMMANDATIONS DES SOCIÉTÉS SAVANTES	
SCP (Robinson *et al.*, 2015)	Maximum de trois à cinq doses par saison (15 mg/kg/dose), quatre doses étant probablement suffisantes pour tous les groupes à risque, si le palivizumab est administré seulement en présence d'activité du VRS dans la collectivité, particulièrement si les deuxième, troisième et quatrième doses sont administrées à 38 jours d'intervalle. Il n'y a aucune preuve soutenant l'administration de plus de cinq doses en une seule saison du VRS.
AAP, 2014	Maximum de cinq doses à raison de 15 mg/kg à chaque mois durant la saison du VRS. Les enfants nés durant celle-ci en requerraient moins.
DOCUMENTATION SCIENTIFIQUE RETENUE	
Feltes *et al.*, 2003.	
OPINION DES MEMBRES DU COMITÉ CONSULTATIF SUR LE PALIVIZUMAB ET RECOMMANDATION DE L'INESSS	
Saison 2016-2017	- **La date du début et celle de la fin de la saison du VRS devraient faire partie de la circulaire (1er novembre au 31 mars). La période de la saison du VRS au Nunavik est retardée d'un mois par rapport à celle des régions méridionales, soit du 1er décembre au 30 avril.** - **Le palivizumab devrait être administré à raison d'un maximum de quatre doses ou cinq doses par saison, selon la date du début de la prophylaxie propre à**

	l'enfant et celle de la fin de la saison du VRS. • **Une dose additionnelle au cours de la saison du VRS doit être donnée dans le cas des enfants soumis à un processus de circulation sanguine extracorporelle en raison d'une chirurgie.** - **Aucune dose de palivizumab ne devrait être donnée après la date de la fin fixée, sauf dans les circonstances particulières suivantes :** • **Si le VRS est toujours en pleine activité au Nunavik, une dose devrait être administrée en mai aux enfants admissibles au palivizumab qui ont quitté l'hôpital au cours des mois de février à avril après leur naissance.** • **Pour les autres régions du Québec, une dose devrait être administrée en avril à certains prématurés, si le VRS est toujours en pleine activité dans la collectivité. Il s'agit de ceux qui ont quitté l'hôpital au cours des mois de janvier à mars après leur naissance.** - **L'intervalle entre les doses devrait être environ de 28 jours.** - **Un calendrier provincial avec des dates fixes devrait être élaboré et inclus dans la circulaire. Ce calendrier devrait être adapté pour les enfants du Nunavik.**

Conclusion

La poursuite des travaux d'évaluation de l'INESSS en 2016 a permis de réaliser que le mode d'évaluation qu'il adopte usuellement pour des médicaments à inscrire sur les listes de médicaments présente des défis pour un produit à visée préventive comme le palivizumab. Il s'est avéré que les études de qualité et de niveau de preuve élevés sont peu nombreuses et datent de plusieurs années, si bien que leur validité externe est compromise. Le reste de la documentation se limite à de nombreuses études observationnelles qui, pour la plupart, étaient de faible qualité méthodologique. De surcroît, l'usage du palivizumab n'est pas documenté chez certaines populations pédiatriques, jugées à risque d'infection grave par le VRS pour qui des autorisations hors critères avaient été accordées. Enfin, il est peu probable que de bonnes études, ayant pour but de comparer l'effet du palivizumab à un placébo, soient éventuellement menées, à court ou moyen terme, auprès de ces clientèles vulnérables à faible prévalence. Dans un tel contexte, l'INESSS en est arrivé à la conclusion qu'il était quasiment impossible de juger du bien-fondé de l'usage du palivizumab chez les différentes populations identifiées, en se basant sur une approche strictement basée sur des données probantes, comme il le préconise de façon générale. C'est pourquoi il a accordé, dans certaines situations, un poids important à l'opinion des experts spécialisés du Comité consultatif sur l'usage du palivizumab et des sociétés savantes. Il s'agit là d'une démarche exceptionnelle et circonstancielle.

Parmi les recommandations finales, l'INESSS souhaite mettre de l'emphase sur les points suivants :

- L'abrogation du critère concernant les bébés prématurés nés entre 33 et 35 6/7 semaines de grossesse ne semble pas, à première vue, avoir eu de conséquences cliniques significatives chez cette population par rapport à la population pédiatrique globale, et ce, ni sur le nombre d'hospitalisations, ni sur la gravité de l'atteinte durant la saison du VRS 2015-2016. Cependant, l'INESSS croit qu'il est impératif d'évaluer les conséquences du retrait de ce critère sur plusieurs années, parce que les caractéristiques des saisons du VRS varient dans le temps. D'ailleurs la saison dernière a présenté une dynamique particulière, soit un début tardif de la période d'infection et une prévalence importante du virus de l'influenza de type B.

- L'INESSS estime que l'organisation de l'immunoprophylaxie par le palivizumab et des soins prodigués aux enfants résidant au Nunavik est suffisante pour garantir une bonne application de ses recommandations à l'égard des bébés prématurés ou nés à terme. Ces clientèles sont très

vulnérables, car ils présentent plusieurs facteurs de risque d'infection grave par le VRS clairement reconnus de par le monde; elles sont indéniablement parmi celles les plus à risque au Québec. De plus, considérant le vécu communautaire des habitants du Grand Nord et leurs perceptions face aux infections graves qui ont décimé leur peuple dans le passé, l'INESSS est d'avis que ces communautés seront engagées dans un programme d'immunoprophylaxie.

- L'INESSS insiste sur la mise en application de toutes les mesures recommandées ayant pour but de favoriser la persistance de l'effet du palivizumab. De fait, le maintien d'une concentration sérique du palivizumab suffisante pour garantir une prophylaxie constante durant les périodes d'activité intense du VRS est la clé du succès d'un programme d'immunoprophylaxie. Ainsi, le besoin d'un calendrier d'administration et la nécessité d'autoriser une dose additionnelle dans les circonstances particulières décrites précédemment s'imposent.

- Bien qu'il ait été inhabituel d'inclure par le passé des critères d'exclusion dans la circulaire du programme d'immunoprophylaxie, l'INESSS croit que maintenant cette avenue devrait être adoptée pour limiter la soumission inutile de demandes hors critères.

- La mise en place d'un suivi structuré et indépendant des conséquences des nouvelles recommandations est incontournable. Compte tenu du fardeau économique lié aux complications des infections des voies respiratoires par le VRS et à l'immunoprophylaxie, l'INESSS croit essentiel que la tenue d'un registre, qui pourrait s'inspirer de ceux qui sont tenus par d'autres provinces canadiennes, est devenue essentielle. Les difficultés éprouvées pour évaluer l'efficience du palivizumab proviennent en grande partie de l'absence de données comparatives contemporaines québécoises.

SUMMARY

Notice Reevaluation of the eligibility criteria for palivizumab (Synagis) for the 2016-2017 season

On June 2, 2015, the Institut national d'excellence en santé et en services sociaux (INESSS) received a request from the Direction générale des services de santé et de médecine universitaire (DGSSMU) of the Ministère de la Santé et des Services sociaux (MSSS) to reexamine the eligibility criteria for Québec's palivizumab (Synagis®) immunoprophylaxis program for the prevention of respiratory syncytial virus (RSV) infection in infants and young children, with a view to optimizing the use of palivizumab during the 2015-2016 season.

The assessment framework used to carry out this task is based on that established for evaluating drugs for their entry on the lists of insured drugs in Québec. The framework includes the following aspects: the product's therapeutic value, the reasonableness of its price, its cost-effectiveness, the impact on the health of the general public and on the other components of the health and social services system, and other considerations, such as ethical and societal considerations.

Assessment activity (2015-2016 season)

In a timely manner, INESSS was able, among other things, to conduct a targeted review of the scientific literature, to examine the Canadian and American pediatric societies' recommendations, to speak with the product's manufacturer (AbbVie) and to consult a committee of experts. The role of the committee's members was to assist in analyzing the scientific data and to provide clinical expertise in the area of palivizumab immunoprophylaxis in infants and young children at risk for severe RSV infection. The committee consisted mainly of pediatric infectious disease specialists, pediatric respirologists and pediatric cardiologists; pediatricians; neonatologists; and members of the Comité scientifique d'évaluation des médicaments aux fins d'inscription (CSEMI). Special attention was given to the composition of this committee to ensure that its members were from the main integrated university health networks (RUISs), in which vulnerable pediatric patients for whom the immunoprophylaxis examined in this report is intended are treated. Among the members were those asked by Héma-Québec to evaluate nonconforming authorization requests for palivizumab. Despite these various steps, INESSS did not feel that its analysis was thorough enough for it to meet its standards of quality and scientific rigour. There thus emerged a cautious approach that led to the submission of a report containing preliminary proposals (unpublished), which was accompanied by a recommendation to continue its scientific activity with a view to the 2016-2017 season. Actually, a rigorous and thorough scientific analysis of the clinical data was necessary.

It will be noted that changes to the palivizumab utilization criteria for the 2015-2016 were nonetheless made to the Héma-Québec circular on the basis of, among other things, certain preliminary proposals by the advisory committee included in the preliminary report and of the Canadian and American pediatric societies recommendations.

Assessment activity (2016-2017 season)

INESSS conducted a systematic review of the scientific literature [2016, see Appendix I] to identify all the relevant data concerning the following question: What is the prophylactic efficacy of palivizumab in reducing the risk of complications associated with RSV (hospitalizations, long-term sequelae and death) in infants and young children compared to the administration of placebo or to no prophylaxis? The

results taken from the studies included, apart from hospitalizations, intensive care unit stays and the use of assisted ventilation. The research concerned several populations of infants and young children with recognized risk factors for severe infection or a health problem suspected of being one.
In parallel with the systematic review, INESSS identified and analyzed several prospective and retrospective observational cohort studies mainly concerning the impact of using palivizumab in a real-world setting in different countries or the identification of groups of infants and young children with risk factors associated with an increased incidence of hospitalization due to RSV infection.

In addition, INESSS once again consulted the advisory committee, which a pediatrician had joined who specializes in health care in Québec's Far North, that is, the health and social services regions of the Nord-du-Québec, Nunavik and the Terres-Cries-de-la-Baie-James.

The main observations arising from all these steps are as follows:

- The systematic review confirmed the absence of studies involving several of the target populations and the existence of a very small number of quality randomized, controlled studies, whose external validity is diminished by the advances in pediatric health care made over the past few decades. The literature identified in parallel consists mainly of prospective and retrospective observational studies of highly variable quality, from very poor to good. INESSS noticed a major heterogeneity problem with the different studies, which made comparing the results a very difficult task and their application to our clinical context, limited. The most frequent sources of heterogeneity influencing the results include the differences in the characteristics of the RSV seasons according to the region, the lack of uniformity in the practice standards according to the participating centre and their changes over time, and the absence of a control group. Another problem encountered was the lack of statistical power of certain studies that involved a small number of subjects, among others, those with a low-prevalence disease. Lastly, it is unlikely that studies of superior quality will eventually be carried out, especially in the case of rare health problems.

- The revocation of the criterion concerning preterm infants born at 33 to 35 $^{6/7}$ weeks' gestation did not, on the face of it, seem to have had any significant clinical consequences in this population relative to the general pediatric population, either in terms of the number of hospitalizations or the degree of damage, during the 2015-2016 RSV season. However, it is imperative that the consequences of revoking this criterion be evaluated over several years because the characteristics of RSV seasons vary over time. For instance, the last season was marked by a particular set of dynamics, namely, a late start of the infection season and a high prevalence of the influenza type B virus.

- Consulting an expert on the health care available in Québec's Far North provided INESSS with a better understanding of the specific context in this region and enabled it to identify its unmet health-care needs. It is observed that Nunavik infants born at term who do not have any medical risk factors for severe infection that could lead to hospitalization are nonetheless at high risk for developing complications that potentially require a transfer to a university hospital in an urban area. The logistics of air transportation are complex and difficult, especially air transportation from the most remote villages, and can entail risks for the infant because of the wait times for accessing specialized care. Preterm infants of less than 36 weeks' gestational age (GA) in this region constitute another target population. Lastly, the organization of care in Québec's Far North does not seem to be an obstacle to the success of an immunoprophylaxis program adapted to this region.

- Despite the development of a pharmacoeconomic model adapted to Québec, no reliable conclusion could be drawn with respect to the efficiency of palivizumab prophylaxis in the different populations targeted by the recommendations of this report. This can be explained by the weakness of the clinical evidence for some of these populations or by the complete lack of data on others. Consequently, the efficiency of palivizumab could not be evaluated.

- The costs for palivizumab were relatively stable during the 2010-2011 to 2014-2015 seasons, increasing at an average rate of 1.8% per year. They went from $16.8 million in 2014-2015 to $8.9 million in 2015-2016, a decrease of 47%. The number of infants and young children treated decreased by 35%, while the average cost per infant or young child decreased by 18%. During this time, in the rest of Canada, the number of infants and young children treated decreased as well, but only by 9.6%. It should be noted that the number of nonconforming authorizations also decreased in 2015-2016.

- The vulnerability of the populations in question, the anxiety associated with hospitalizing infants and young children, who, in some cases, were hospitalized for a prolonged period at birth, and, lastly, the risks and drawbacks of hospitalization for the infant or young child and his/her family are important considerations.

The assessment of palivizumab immunoprophylaxis using the selected assessment framework was challenging. It concerned a drug intended for preventive rather than curative purposes, and the harm caused by an RSV infection that can cause complications. Its therapeutic value was first examined with regard to the different populations considered to be at risk. It was found that the quality of the available evidence (clinical and epidemiological data) concerning a number of these populations is generally poor or that there is no evidence at all. This is why the opinions of experts and of the Canadian and American pediatric Society had to be taken into account, so that the therapeutic value could be determined by a clinical assessment that INESSS considers entirely acceptable, given the nature of the drug. This said, it was crucially important to form a committee ensuring good representativeness. It will be noted that economic considerations were not taken into account when assessing the drug's therapeutic value. From the moment the scientific or clinical relevance of using palivizumab was established, INESSS examined all the considerations pertaining to the reduction of the harm associated with RSV infection, which can become complicated to the point of requiring hospitalization of the affected individual. The recommended overall approach is, in INESSS's opinion, the best level of evidence that can support the recommendations formulated in this report.

The following tables summarize INESSS's recommendations regarding the use of palivizumab for the 2016-2017 RSV season in the different populations and the details of its administration.

Preterm infants with no risk factors other than prematurity

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	**Criterion No. 1** Infants born at <33 weeks' gestation and <6 months of age at the start of the RSV season.
2015-2016 season	**Criterion No. 1** Infants born at <33 weeks' gestation and <6 months of age at the start of the RSV season.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Although not essential, in preterm infants without bronchopulmonary dysplasia, only if they were born before 30 weeks' gestation and are <6 months of age at the start of the RSV season.
AAP, 2014	In preterm infants, only if they were born at <29 weeks' gestation and are <12 months of age at the start of the RSV season.
SCIENTIFIC LITERATURE CONSULTED	
Notario *et al.*, 2014; Andabaka *et al.*, 2013; Tavsu *et al.*, 2013; Checchia *et al.*, 2011; Grimaldi *et al.*, 2007; IMpact-RSV, 1998.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the 2015-2016 criterion should be maintained.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the 2015-2016 criterion: Infants born at <33 weeks' gestation and <6 months of age at the start of the RSV season.**

Preterm infants with risk factors identified by Sampalis [2008]

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	**Criterion No. 2** Infants born at 33 to 35 $^{6/7}$ weeks' gestation and who are <6 months of age at the start of the RSV infection season and have a score >48 on the risk scale presented by Sampalis (2008).
2015-2016 season	Criterion revoked.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Palivizumab prophylaxis is not recommended.
AAP, 2014	
SCIENTIFIC LITERATURE CONSULTED	
Anderson *et al.*, 2016; analyse regroupée d'Anderson (manuscript under peer review); Ryan *et al.*, 2016; Stranak *et al.*, 2016; Ambrose *et al.*, 2014 (REPORT); Notario *et al.*, 2014; Blanken *et al.*, 2013; Mitchell *et al.*, 2011 (CARESS); Paes *et al.*, 2009, Mitchell *et al.*, 2006; Law *et al.*, 2004; Wegner *et al.*, 2004; IMpact-RSV, 1998.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
Most of the members are of the opinion that the revocation of the 2014-2015 criterion be maintained on the condition that an objective and independent process is put in place to monitor this population.	
INESSS'S RECOMMENDATION	

2016-2017 season	**Maintain the revocation of the 2014-2015 criterion on the condition that an independent, structured monitoring of these infants' outcome is put in place.**

Children with bronchopulmonary dysplasia or chronic lung disease of the newborn

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	**Criterion No. 3** Children <24 months of age with: • a chronic lung disease; or • a medical condition with severe respiratory complications; **<u>and</u>** • who required oxygen during the 6 months preceding the RSV season; or • who require oxygen during the RSV season.
2015-2016 season	**Criterion No. 2** Children <24 months of age at the start of the RSV season who have chronic lung disease of the newborn (defined as the need for oxygen at 36 weeks' gestational age) or bronchopulmonary dysplasia (defined as the need for oxygen at 28 days of life and until at least 36 weeks' gestational age) **and:** • who required oxygen during the 6 months preceding the RSV season; or • who require oxygen during the RSV season.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	During the first year of life of infants <12 months of age at the start of the RSV season who have chronic lung disease of prematurity (defined as the need for oxygen at 36 weeks' GA) and who have an ongoing need for diuretics, bronchodilators, steroids or supplemental oxygen. During the second year of life of children aged 12 months to <24 months before the start of the RSV season who have chronic lung disease of prematurity (defined as the need for oxygen at 36 weeks' GA), who are still on oxygen or who were weaned from it during the 3 months preceding the current RSV season.
AAP, 2014	During the first year of life of preterm infants who develop chronic lung disease of prematurity defined as gestational age <32 $^{0/7}$ weeks and a requirement for >21% oxygen for at least the first 28 days after birth. During the second year of life of infants who satisfy the above definition of chronic lung disease of prematurity and who continue to require treatment (chronic corticosteroid therapy, diuretic therapy or oxygen) during the 6 months preceding the start of the second RSV season.
SCIENTIFIC LITERATURE CONSULTED	
Notario *et al.*, 2014; Mitchell *et al.*, 2011 (CARESS); Chang *et al.*, 2010; Mitchell *et al.*, 2006; Grimaldi *et al.*,	

2004; Pedraz *et al.*, 2003; Boyce *et al.*, 2000; IMpact-RSV 1998.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the 2015-2016 criterion should be modified to make it easier to understand.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Modification of the 2015-2016 criterion:** - **Term or near-term children <24 months of age at the start of the RSV season who have chronic lung disease of the newborn, defined as the need for oxygen therapy at birth that has persisted because of chronic lung damage other than that mentioned in the other criteria;** **or** - **Preterm children <24 months of age at the start of the RSV season with bronchopulmonary dysplasia, defined as the need for oxygen therapy shortly after birth that persists up to at least 28 days of life and up to a gestational age of at least 36 weeks, with the presence of a characteristic history of the disease;** **and** - **who have required ongoing chronic oxygen therapy during the 6 months preceding the start of the RSV season or who require oxygen therapy during the RSV season.**

Children with cystic fibrosis

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	**Criterion No. 3** Children <24 months of age with: • a chronic lung disease; **or** • a medical condition with severe respiratory complications; **and** • who required oxygen during the 6 months preceding the RSV season; **or** • who require oxygen during the RSV season. Certain cases authorized upon a nonconforming request.
2015-2016 season	**Criterion No. 3** Infants <24 months of age at the start of the RSV season with cystic fibrosis who present with significant respiratory symptoms or failure to thrive.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*,2015)	Palivizumab should not be administered routinely to children with cystic fibrosis. It may, however, be considered in the following cases:

	Children <24 months of age with cystic fibrosis, only if they are on home oxygen, if they have had a prolonged hospitalization for severe pulmonary disease or are severely immunocompromised.
AAP , 2014	Palivizumab should not be administered routinely to children with cystic fibrosis. It may, however, be considered in the following cases: During the first year of life of an infant with cystic fibrosis with clinical evidence of chronic lung disease or failure to thrive. During the second year of life of a child with cystic fibrosis who received palivizumab during his/her first year, if he/she has signs of a serious medical condition (hospitalization for pulmonary exacerbation during the first year of life or abnormalities on chest radiography or computed tomography that persist when the disease is stable) or if he/she presents with failure to thrive ($\leq 10^{th}$ percentile).
SCIENTIFIC LITERATURE CONSULTED	
Groves *et al.*, 2016; Robinson *et al.*, 2014; Winterstein *et al.*, 2013; Giebels *et al.*, 2008.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the 2015-2016 criterion should be maintained.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the 2015-2016 criterion: Children <24 months of age at the start of the RSV season with cystic fibrosis who present with significant respiratory symptoms or failure to thrive.**

Children with neuromuscular disorders

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No criterion. Certain cases authorized upon a nonconforming request.
2015-2016 season	**Criterion No. 4** Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of a neuromuscular disorder.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Palivizumab should not be administered routinely to children with an upper airway obstruction. However, this drug may be considered for children <24 months of age who are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease or are severely immunocompromised.
AAP, 2014	Palivizumab may be administered during the first year of life of infants with a neuromuscular disease whose manifestations reduce the ability to clear upper airway secretions because of ineffective cough, since it is known that they are at risk for a prolonged hospitalization in the event of a severe lower respiratory tract infection.
SCIENTIFIC LITERATURE CONSULTED	
Kristensen *et al.*, 2012; Zachariah *et al.*, 2011.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the 2015-2016 criterion should be maintained.	
INESSS'S RECOMMENDATION	

2016-2017 season	**Maintain the 2015-2016 criterion: Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of a neuromuscular disorder. The diagnosis must be indicated on the request.**

Children with congenital anomalies of the upper respiratory tract

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No criterion. Certain cases authorized upon a nonconforming request.
2015-2016 season	**Criterion No. 5** Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of congenital anomalies of the upper respiratory tract.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Palivizumab should not be administered routinely to children with an upper airway obstruction. However, this drug may be considered for children <24 months of age who are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease or are severely immunocompromised.
AAP, 2014	Palivizumab may be administered during the first year of life of infants with a congenital anomaly that reduces the ability to clear upper airway secretions because of ineffective cough, since it is known that they are at risk for a prolonged hospitalization in the event of a severe lower respiratory tract infection.
SCIENTIFIC LITERATURE CONSULTED	
Kristensen *et al.*, 2012; Zachariah *et al.*, 2011.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the 2015-2016 criterion should be maintained.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the 2015-2016 criterion: Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of a congenital anomaly of the upper airways. The diagnosis must be indicated on the request.**

Children with heart disease

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	**Criterion No. 4** Children <24 months of age with hemodynamically significant congenital heart disease.
2015-2016 season	**Criterion No. 6** Infants <12 months of age at the start of the RSV season with hemodynamically significant congenital heart disease, cardiomyopathy or myocarditis or with moderate to severe pulmonary hypertension (the request must be submitted by a pediatric cardiologist to ensure the accuracy of the diagnosis).

RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Infants <12 months of age at the start of the RSV season with hemodynamically significant congenital heart disease.
AAP, 2014	In infants <12 months of age at the start of the RSV season with hemodynamically significant congenital heart disease, including: • Infants with acyanotic heart disease who are on medication to control congestive heart failure and who will require cardiac surgery. • Infants with moderate to severe pulmonary hypertension.
SCIENTIFIC LITERATURE CONSULTED	
Harris *et al.*, 2011; Bellavance *et al*., 2006; Feltes *et al*., 2003; Boyce *et al*., 2000; Wang *et al*., 1997.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the 2015-2016 criterion should be maintained.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the 2015-2016 criterion: Children <12 months of age at the start of the RSV season who have hemodynamically significant congenital heart disease, cardiomyopathy or myocarditis or moderate to severe pulmonary hypertension (the request must be submitted by a pediatric cardiologist to ensure the accuracy of the diagnosis).**

Immunocompromised children

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	**Criterion No. 5** Children <24 months of age who have undergone a bone marrow or stem cell transplant during the 6 months preceding the RSV season or during the RSV season. Certain cases authorized upon a nonconforming request.
2015-2016 season	**Criterion No. 7** Children <24 months of age at the start of the RSV season who have undergone a bone marrow, stem cell or solid-organ (heart, liver or lung) transplant during the 6 months preceding the RSV season or during the RSV season.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Palivizumab should not be administered routinely to children with immune deficits, with the exception of those <24 months of age who are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease or are severely immunocompromised.
AAP, 2014	Palivizumab may be administered to children <24 months of age who, during the RSV season, are severely immunocompromised or are to undergo a heart transplant.
SCIENTIFIC LITERATURE CONSULTED	
Asner *et al.*, 2013; El Saleeby *et al.*, 2008; Hall *et al.*, 1986.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the 2015-2016 criterion should be maintained.	
INESSS'S RECOMMENDATION	

Saison 2016-2017	**Maintain the 2015-2016 criterion: Children <24 months of age at the start of the RSV season who have undergone a bone marrow, stem cell or solid-organ (heart, liver or lung) transplant during the 6 months preceding the RSV season or during the RSV season.**

Infants in remote communities

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No criterion. Certain cases authorized upon a nonconforming request.
2015-2016 season	No criterion. Certain cases authorized upon a nonconforming request.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Palivizumab should be offered to infants in remote communities born before 36 weeks' gestational age and <6 months of age at the start of the RSV season who would require air transportation for hospitalization. It is not clear whether this recommendation should apply only to Inuit infants, to all Aboriginal infants or to all infants in remote communities.
AAP, 2014	The use of palivizumab for the Alaska Native population or for Amerindian populations on US territory is not formally recommended. However, the burden associated with severe RSV infections and the costs associated with air transportation required for hospitalizing children with such infections living in remote communities could justify a broader use of palivizumab in these populations.
SCIENTIFIC LITERATURE CONSULTED	
Banerji *et al.*, 2014; Banerji *et al*., 2013; Singleton *et al.*, 2003.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that criteria should be added for infants born at ≤36 weeks' gestational age who are <6 months of age at the start of the RSV season and who live in a remote area where access to health care in the event of a serious medical condition would require air transportation and for those born at term who are <3 months of age at the start of the RSV season and who live in a remote area where access to health care in the event of a serious medical condition would require air transportation.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Additional criteria:** - **Nunavik infants born at ≤36 weeks' gestational age who are <6 months of age at the start of the RSV or born during the RSV season.** - **Nunavik infants born at term and who are <3 months of age at the start of the RSV season or born during the RSV season.**

Children with Down syndrome

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No criterion. Certain cases authorized upon a nonconforming request.
2015-2016 season	No criterion. No known cases authorized upon a nonconforming request.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Palivizumab should not be administered routinely to children with Down syndrome. It may be reasonable to do so to those <24 months of age at the start of the RSV season

	and who are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease or are severely immunocompromised.
AAP, 2014	Children with Down syndrome if they have heart disease, chronic lung disease or impaired clearance of airway secretions or were born preterm at <29 weeks' GA.
SCIENTIFIC LITERATURE CONSULTED	
Yi *et al.*, 2014.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that no criteria should be added for this population.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the absence of criteria.**

Children with a metabolic disease

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No criterion. Certain cases authorized upon a nonconforming request.
2015-2016 season	No criterion. No known cases authorized upon a nonconforming request.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	No recommendations concerning this population are provided.
AAP, 2014	
SCIENTIFIC LITERATURE CONSULTED	
Kristensen *et al.*, 2012.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that no criteria should be added and that the nonconforming authorization process be maintained on a case-by-case basis, subject to a review of the list of diseases involving the highest risk of severe decompensation.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the absence of criteria.**

Infants of a multiple birth

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No criterion. Certain cases authorized upon a nonconforming request.
2015-2016 season	No criterion. No known cases authorized upon a nonconforming request.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	No recommendations concerning this population are provided.
AAP, 2014	
SCIENTIFIC LITERATURE CONSULTED	
None	

OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that no criteria should be added and that the administration of palivizumab to healthy twins of infants who qualify for palivizumab through the nonconforming authorization process no longer be authorized.	
INESSS'S RECOMMENDATION	
Saison 2016-2017	**Maintain the absence of criteria.**

Children 24 months of age or older

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No criterion. Cases refused upon a nonconforming request.
2015-2016 season	No criterion. Cases refused upon a nonconforming request.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	The administration of palivizumab to children ≥24 months of age at the start of the RSV season is not recommended.
AAP, 2014	
SCIENTIFIC LITERATURE CONSULTED	
None	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that the use of palivizumab in this population should not be authorized.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the absence of criteria.** **Include a statement of exclusion in the circular.**

Continuing to administer palivizumab after the occurrence of RSV infection

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No mention in the circular.
2015-2016 season	Prophylaxis should be discontinued if RSV infection has been confirmed in the infant or young child.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Continuing to administer palivizumab after the occurrence of confirmed RSV infection is not recommended.
AAP, 2014	
SCIENTIFIC LITERATURE CONSULTED	
None	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that palivizumab should not continue to be used after the occurrence of confirmed RSV infection in infants or young children whose condition has required hospitalization.	

INESSS'S RECOMMENDATION	
2016-2017 season	**Maintain the statement in the circular, with changes: Palivizumab prophylaxis should be discontinued after an infant or young child has been hospitalized for an RSV respiratory tract infection that has been confirmed by a screening test.**

Administration of palivizumab during hospitalization

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	No mention in the circular.
2015-2016 season	No mention in the circular.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	Start palivizumab just before discharge from hospital. Palivizumab is not recommended for the prevention of nosocomial infections.
AAP, 2014	Start palivizumab just before discharge from hospital or very shortly thereafter.
SCIENTIFIC LITERATURE CONSULTED	
None	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE	
The members are unanimously of the opinion that palivizumab should be administered to an infant who qualifies for it 48 to 72 hours before his/her discharge and that the date for the second dose should, at that point, be set immediately.	
INESSS'S RECOMMENDATION	
2016-2017 season	**Include the following two statements in the circular:** - **Palivizumab should be administered 48 to 72 hours before an infant who qualifies for it is discharged from hospital after birth.** - **Administering palivizumab to prevent nosocomial RSV infections is not recommended.**

Details of administration of palivizumab

QUÉBEC ELIGIBILITY CRITERIA	
2014-2015 season	The recommended administration schedule for palivizumab immunization is every 4 weeks, starting in November. Normally, 5 doses should be administered per season, with a maximum of 6 doses, if necessary.
2015-2016 season	The recommended administration schedule for palivizumab immunization is every 4 weeks, starting in mid-November. A maximum of 5 doses should be administered per season, the last dose not to be administered after the month of March.
RECOMMENDATIONS OF LEARNED SOCIETIES	
CPS (Robinson *et al.*, 2015)	A maximum of 3 to 5 doses per season (15 mg/kg/dose), 4 doses probably being sufficient for all at-risk groups if palivizumab is administered only in the presence of RSV activity in the community, especially if the second, third and fourth doses are administered at 38-day intervals. There is no evidence supporting the administration of more than 5 doses in a single RSV season.

AAP, 2014	A maximum of 5 doses at the rate of 15 mg/kg each month during the RSV season. Infants born during the RSV season would require less.
SCIENTIFIC LITERATURE CONSULTED	
Feltes *et al.*, 2003.	
OPINION OF THE MEMBERS OF THE PALIVIZUMAB ADVISORY COMMITTEE AND INESSS'S RECOMMENDATION	
2016-2017 season	- **The start and end dates of the RSV season should be indicated in the circular (November 1 to March 31). In Nunavik, the RSV season starts a month later than in southern regions, extending from December 1 to April 30.** - **Palivizumab should be administered at a rate of no more than 4 or 5 doses per season, depending on the prophylaxis start date specific to the child and the end date of the RSV season.** • **An additional dose during the RSV season should be administered to children undergoing extracorporeal blood circulation for surgical purposes.** - **No palivizumab doses should be administered after the set end date, except in the following special circumstances:** • **If there is still strong RSV activity in Nunavik, one dose should be administered in May to infants eligible for palivizumab discharged from hospital in February, March or April after their birth.** • **For the other regions of Québec, one dose should be administered in April to certain preterm infants if there is still strong RSV activity in the community, specifically, those discharged from hospital in January, February or March after their birth.** - **The dosing interval should be approximately 28 days.** - **A provincial calendar with set dates should be created and included in the circular. The calendar should be adjusted for Nunavik infants.**

Conclusion

Upon continuing its assessment activity in 2016, INESSS realized that the assessment method that it usually uses for drugs to be entered on the lists of medications poses challenges when applied to a prophylactic drug like palivizumab. It was found that the studies of high quality and of a high level of evidence are scarce and were carried out many years ago, with the result that their external validity is compromised. The rest of the literature consists only of numerous observational studies, which, for the most part, were of low methodological quality. Furthermore, the use of palivizumab is not documented in certain pediatric populations considered at risk for severe RSV infection and for which nonconforming authorizations had been granted. Lastly, it is unlikely that good studies aimed at comparing the effect of palivizumab with that of placebo will eventually be conducted in the short or medium term in these vulnerable, low-prevalence groups. This said, INESSS concluded that it was nearly impossible to assess the merits of using palivizumab in the different populations identified, using a strictly evidence-based approach, as it generally recommends. This is why, in certain situations, it accorded significant weight to the opinion of the specialized experts on the Advisory Committee on the Use of Palivizumab and the opinions of the learned societies. This was an exceptional and circumstantial approach.

INESSS would like to emphasize the following points in its recommendations:

- The revocation of the criterion concerning preterm infants born at 33 to 35 $^{6/7}$ weeks' gestation did not, on the face of it, seem to have had any clinically significant consequences in this population compared to the general pediatric population, either in terms of the number of hospitalizations or

the degree of damage, during the 2015-2016 RSV season. However, INESSS feels that it is imperative to evaluate the consequences of revoking this criterion over several years because the characteristics of RSV seasons vary over time. For instance, the last season was marked by a particular set of dynamics, namely, a late start of the infection period and a high prevalence of the influenza type B virus.

- INESSS believes that the organization of palivizumab immunoprophylaxis and of the care provided to Nunavik infants is adequate to ensure the proper application of its recommendations regarding term and preterm infants. These infants are highly vulnerable because they have several risk factors for severe RSV infection that are clearly recognized worldwide. They are unquestionably among the populations most at risk in Québec. Furthermore, given the community experience of residents of the Far North and their perceptions of the serious infections that have decimated their people in the past, INESSS feels that these communities will be engaged in an immunoprophylaxis program.

- INESSS emphasizes applying all the recommended measures aimed at prolonging palivizumab's effect. Indeed, maintaining a high enough serum palivizumab concentration to ensure ongoing prophylaxis during periods of intense RSV activity is the key to the success of an immunoprophylaxis program. Therefore, there is a need for an administration schedule and to authorize an additional dose in the special circumstances mentioned above.

- Although it was, in the past, unusual to include exclusion criteria in the circular for the immunoprophylaxis program in the past, INESSS believes that this approach should now be adopted to limit the pointless submission of nonconforming requests.

- Putting in place structured, independent monitoring of the consequences of the new recommendations is a must. Given the economic burden associated with the complications of RSV respiratory tract infections and with immunoprophylaxis, INESSS believes that it is now essential to maintain a registry, which could be modelled after those maintained by other Canadian provinces. The difficulties encountered in evaluating the efficiency of palivizumab are due, in large part, to the absence of contemporary comparative data for Québec.

1. INTRODUCTION

With a view to optimizing the use of palivizumab and to subsequently determining the budget to be allocated to it, the MSSS asked INESSS to review the eligibility criteria in Québec's palivizumab immunoprophylaxis program. The recent publication of new US and Canadian guidelines was the main incentive for reviewing this matter, followed by the increasing number of requests for palivizumab for off-label indications.

The palivizumab (Synagis®) is a passive immunization agent, more precisely, a humanized monoclonal antibody (IgG1κ), marketed as a powder for intramuscular injection. On March 6, 2015, a new formulation in the form of a solution for intramuscular injection received a notice of compliance from Health Canada. This formulation should be available during the 2016-2017 RSV season at no additional cost. It will be easier to use, since it will be ready to use, unlike the powder, which has to be reconstituted and administered after standing for 20 minutes. Palivizumab acts by neutralizing the RSV and inhibits its fusion. It is indicated "for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease". It will be noted that palivizumab does not prevent RSV transmission. Rather, it has an impact on the risk of RSV infection worsening to the point that the affected child requires hospitalization.

RSV is the leading cause of lower respiratory tract illnesses, notably, bronchiolitis and pneumonia, in young children. Their incidence peaks in infants aged 2 to 6 months, and the virus infects almost all children before the age of 2 years during annual epidemics that generally occur in Québec from mid-November to late April. The treatment of affected children consists mainly of symptomatic relief. The primary infection does not confer any protective immunity, and reinfection can occur during the same season or during subsequent seasons.

Approximately 1 to 2% of children with bronchiolitis will be so sick that they will have to be hospitalized in order to receive oxygen therapy, intravenous fluids or other supportive care. Hospitalization costs account for more than half of the economic burden associated with RSV in children <4 years of age. The scientific literature reports that certain pediatric populations are at greater risk than others for being hospitalized, for staying in hospital longer or for being admitted to an intensive care unit. They are mainly certain preterm infants, children with bronchopulmonary dysplasia, chronic lung disease of the newborn or hemodynamically significant congenital heart disease. Some of the hospitalized children may have long-term sequelae, such as wheezing or asthma. Deaths are not frequent.

Québec has had an immunoprophylaxis program since June 2005. It is intended for pediatric populations considered to be at greatest risk for complications during RSV respiratory tract infection.

The objective of this report is to review INESSS's recommendations concerning the update of the eligibility criteria in this program for the 2016-2017 season and the details of administration of palivizumab in light of the advances in science and clinical practice.

2. OVERVIEW OF THE EVOLUTION OF QUÉBEC'S IMMUNOPROPHYLAXIS PROGRAM

June 2005	Recommendation for the first palivizumab eligibility criteria.
June 2006 and 2009	Modification of the palivizumab eligibility criteria.
August 2015	Reevaluation of the eligibility criteria and submission of an unpublished preliminary report.
September 2015	Modification of the palivizumab eligibility criteria by the MSSS.

The palivizumab eligibility criteria that INESSS used during its fourth evaluation of Synagis® are those that had been in effect during the 2014-2015 RSV season, namely:

1. Infants born at <33 weeks' gestation and <6 months of age at the start of the RSV season;
2. Infants born between 33 and 35 $^{6/7}$ weeks' gestation who are <6 months of age at the start of the RSV infection season and have a score >48 on the Sampalis risk scale [2008];
3. Children <24 months of age with:

   a chronic lung disease;

   or

   a medical condition with severe respiratory complications;

   and

   who require oxygen therapy during the 6 months preceding the RSV season;

   or

   who require oxygen therapy during the RSV season;
4. Children <24 months of age with hemodynamically significant congenital heart disease;
5. Children <24 months of age who have had a bone marrow transplant or a stem cell transplant within the 6 months preceding the RSV season or during the RSV season.

Although the MSSS modified the eligibility criteria for the last season (2015-2016), the starting point of the following assessment was the criteria for the 2014-2015 season because these were the criteria that were in effect when INESSS began work on this dossier.

3. METHODOLOGY

INESSS carried out work to reevaluate the eligibility criteria for palivizumab for the prevention of severe RSV respiratory tract infections in children. To this end, the assessment framework used in 2015 was modeled after that on that established for evaluating drugs for the purpose of entering them in the lists of insured medications in Québec. It includes the following aspects: therapeutic value, the reasonableness of the price and the product's cost-effectiveness, the impact on the health of the population and on the other components of the health and social services system, and other considerations, such as of an ethical or societal nature. It is a rigorous approach for making evidence-based recommendations, in addition to taking into account the availability of all types of resources and ethical considerations. This increases the chances that the medical community will adhere to these recommendations and that the population will be receptive to the changes, if applicable.

The work was done in two phases because of the complexity of the task and the different dimensions that needed to be considered to make relevant recommendations concerning the use of palivizumab.

Here are the main tasks performed during these two phases:

Phase I (2015)

- Request to the manufacturer of Synagis® for its cooperation in providing any documentation relevant to the reevaluation of palivizumab.
- Preliminary analysis by INESSS of all the documentation gathered.
- Evaluation of certain nonconforming requests for palivizumab.
- Creation and first meeting of the Advisory Committee on the Use of Palivizumab, the list of whose members is provided in Appendix II of this report (it included, among others, 12 physicians from various specialties and 3 experts from the INESSS's CSEMI).
- Development of a pharmacoeconomic model specific to INESSS and determination of the hypotheses to be validated from the perspective of the Québec context.
- Presentation, to the CSEMI's members, of the report on the Advisory Committee's work, including its proposals and arguments.
- Drafting and submission of a preliminary report to the MSSS setting out some of INESSS proposals, subject to the continuation of a more in-depth analysis of the scientific literature, this with a view to implementation for the 2016-2017 season.

Phase II (2016)

- Systematic review of the scientific literature aimed at evaluating the efficacy of palivizumab in reducing the complications associated with RSV respiratory tract infections (RTIs).
- Second meeting of the Palivizumab Advisory Committee, the list of whose members, provided in Appendix II, changed slightly because of the personal constraints of some of its members.
- Consultation of a pediatrician specializing in health care in Québec's Far North.
- Continuation of the analysis of the scientific literature on palivizumab, including that provided by the manufacturer, with a view to making final recommendations concerning its use and evaluating

its cost-effectiveness and the impact on the health of the population and on the other components of the health-care system, and the other considerations, namely those of an ethical or societal nature.

- Presentation, to the CSEMI's members, of the report on the Advisory Committee's second meeting for the purpose of finalizing its assessment and making final recommendations.
- Drafting and submission of the final report.

For phase II of its work, INESSS considered it necessary to perform a literature review in order to identify all the publications concerning the effect of palivizumab prophylaxis in reducing RSV hospitalizations among at-risk children compared to the administration of placebo or to no prophylaxis. At the same time, INESSS identified several prospective and retrospective observational cohort studies that mainly concerned the impact of using palivizumab in a real-world context in different countries or the identification of pediatric populations with risk factors associated with an increased incidence of RSV hospitalization. More than 150 publications were examined with a view to selecting the most relevant ones. About 30 of them, together with several other documents of interest, were submitted to the Advisory Committee on the Use of Palivizumab for its assessment. In general, the experts consulted found the level of evidence of these publications to be low.

Further analysis of the scientific data revealed the absence of studies on certain populations of interest and that only a small number of quality randomized controlled studies were available. Furthermore, INESSS encountered a major problem of heterogeneity between the different studies, which made comparing their results very difficult and their extrapolation to our clinical context, limited. The most frequent sources of heterogeneity affecting the results were as follows:

- The length of the RSV season varies from country to country and even between regions within a given country. The same is true for the duration of observation in these studies.
- Screening tests were seldom performed routinely, and the different tests used did not all have the same sensitivity.
- The practice standards were not uniform in the different centres that participated in the studies, in addition to the fact that they have changed over time.
- The design of most of the studies does not include a control group.
- The confounding variables taken into consideration in the statistical analyses differ, among other things, in nature and number, or they were simply not taken into account.

Given the foregoing, it was quite unfeasible to use a strictly evidence-based approach to assess the relevance of making immunoprophylaxis available to certain pediatric populations. This is why the opinions of the Advisory Committee on the Use of Palivizumab and those of learned societies were considered sufficient in a number of cases to make recommendations.

4. REVIEW OF THE IMMUNOPROPHYLAXIS PROGRAM

4.1 RELEVANCE OF USING PALIVIZUMAB IN DIFFERENT POPULATIONS

4.1.1 Preterm infants with no risk factors other than prematurity

A. Québec eligibility criteria

2014-2015 season	**Criterion No. 1** Infants born at <33 weeks' gestation and <6 months of age at the start of the RSV season.
2015-2016 season	**Criterion No. 1** Infants born at <33 weeks' gestation and <6 months of age at the start of the RSV season.

B. Background

The evidence on which Criterion No. 1 (above) is based is from the IMpact-RSV study [1998], a randomized, double-blind, placebo-controlled, multicentre study. One of the study populations consisted of infants born at ≤35 weeks' gestation who had no other medical factor that can increase the risk of hospitalization for an RSV RTI, such as heart disease or bronchopulmonary dysplasia. The other population consisted of children <24 months of age with bronchopulmonary dysplasia requiring treatment. The main results comparing the group of children who received palivizumab and the group that received placebo are as follows:

- The hospitalization rate among the preterm infants who received palivizumab was 1.8% compared to 8.1% among those who received placebo, for a reduction in the relative risk of hospitalization in relation to placebo of 78% (95% CI: 66% to 90%; p <0.001).
- The reduction in the relative risk of hospitalization among the children of <32 weeks' GA who received palivizumab compared to those who received placebo was 47% (p = 0.003).
- For all the Canadian infants recruited, the RSV hospitalization rate was 8.8% in those who received palivizumab and 14.7% in those who received placebo, or a 40% reduction in the relative risk of hospitalization.

This study was considered to be of good methodological quality, and its level of evidence was considered high. The results clearly showed the superiority of palivizumab in relation to placebo in reducing hospitalizations in cases of severe RSV infection in the total population. However, it will be noted that the hospitalization rates were higher among the children recruited in Canada than in those in the total population, this for each subpopulation. In addition, the benefits of palivizumab seemed to be less pronounced in the Canadian infants.

By way of information, it will be noted that Notario [2014] recently performed a *post hoc* analysis of the IMpact-RSV study aimed at evaluating the efficacy of palivizumab in relation to that of placebo by stratifying the cohort of 727 preterm infants into 11 GA subgroups. The results for the infants concerned by Criterion No. 1 were as follows:

- Of the infants of <29 weeks' GA, 2% (2/102) of those who received palivizumab were hospitalized compared to 10% (4/40) of those who received placebo, for a non-statistically significant reduction in the relative risk of hospitalization (80.4%; 95% CI: -8.3% to 97.4%).
- Of the infants of 29 to 32 weeks' GA, 1.6% (4/256) of those who received palivizumab were hospitalized compared to 8.2% (9/117) of those who received placebo, for a 79.7% reduction in the relative risk of hospitalization (95% CI: 35.7% to 96.9%).

In short, the results of Notario's analysis showed the superiority of palivizumab prophylaxis to the administration of placebo in reducing the incidence of hospitalizations in the subgroup of infants of 29 to 32 weeks' GA. No difference was observed in the subgroup of infants born at <29 weeks' gestation. INESSS believes that this conclusion is uncertain because the analysis had not been planned beforehand in the IMpact-RSV study and because this study was not designed in such a way as to ensure sufficient statistical power to detect a difference in the subgroups stratified by GA. Nonetheless, it is interesting to know the absolute hospitalization rates and to compare them with those observed in more recent studies. Although the IMpact-RSV study was of good quality, INESSS feels that its external validity is diminished as a result of the substantial advances in neonatology care and because of the changes in practice standards since 1998.

In 2015, the members of the Advisory Committee on the Use of Palivizumab unanimously proposed maintaining Criterion No. 1.

C. Scientific publications selected

Guidelines of the American Academy of Pediatrics [AAP, 2014] and the Canadian Paediatric Society [Robinson et al*., 2015]*

As regards cases of extreme or severe prematurity, the recent guidelines of these two learned societies differ. Since 2014, the AAP Committee on Infectious Diseases has recommended palivizumab immunoprophylaxis in preterm infants only if their GA is <29 weeks and they are <12 months of age at the start of the RSV season. As for the CPS [Robinson *et al.*, 2015], without considering palivizumab immunoprophylaxis indispensable, it now recommends it for preterm infants who do not have bronchopulmonary dysplasia only if their GA is <30 weeks and they are <6 months of age at the start of the RSV season.

INESSS's systematic review of the scientific literature [2016]

Checchia's meta-analysis [2011], which is of average methodological quality, is not very useful because the analysis grouped together studies whose populations and methodologies were too heterogeneous, which compromises the reliability of the results. As for Andabaka's meta-analysis [2013], which is of good methodological quality, the final results are based on those of only two of the identified studies, which raises doubts as to the relevance of this meta-analysis. Given the foregoing, an individual analysis of the studies identified in the systematic review was recommended instead. Of these studies, the only ones whose methodological quality is considered sufficient are the IMpact-RSV study [1998], which was examined above, and those by Grimaldi [2007] and Tavsu [2013].

The objective of Grimaldi's study [2007], a French observational study, was to evaluate the efficacy of palivizumab in preterm infants of ≤30 weeks' GA who did not have bronchopulmonary dysplasia, defined as the persistent need for oxygen therapy up to at least 28 days of life, by comparing a prospective cohort and a retrospective cohort. Included in this study were all infants hospitalized for bronchiolitis caused by RSV confirmed by a routine screening test during five RSV seasons, from December to April from 1999 to 2003, if they were born during the period from April 15 to January 31 and were <6 months of age at the start of the RSV season. Palivizumab was not administered during the 1999, 2000 and 2001 RSV seasons (historical cohort), but it was during the last two RSV seasons (prospective cohort). The main results were as follows:

- In the absence of palivizumab immunoprophylaxis, 13.5% (16/118) of the infants were hospitalized compared to 2% (1/70) of those who received palivizumab, that is, an absolute difference of 11.5% ($p < 0.0001$) showing palivizumab's superior efficacy in reducing the incidence of RSV hospitalizations.
- The number of subjects (infants) to be treated to prevent one hospitalization (NNT) was 6 (95% CI: 4 to 11).

This study is considered to be of poor methodological quality. One of its main limitations is the absence of predefined, uniform criteria for hospitalizing an infant. Furthermore, hospital pediatricians were directly involved in prospectively recording the bronchiolitis clinical data, which may have constituted an additional source of bias. Nonetheless, certain positive aspects are to be noted, such as having routinely performed screening tests and having continued with the same type of test in a given hospital during the five RSV seasons, which limited bias due to variations in RSV detection sensitivity. Furthermore, palivizumab was systematically administered to the infants before their discharge from hospital after birth if they met the above-mentioned requirements, except in cases of parental refusal. This increased the chances of obtaining a complete cohort. The results indicated a high hospitalization rate in the absence of immunoprophylaxis, which suggests that severely premature infants are at very high risk for severe RSV infection. Although this method of comparison is imperfect, the hospitalization rate obtained in this study appears to be higher than those observed in the subgroups of preterm infants in the IMpact-RSV study with a GA <29 weeks or that varied from 29 to 30 weeks and reported by Notario. The same is true for the size of the difference between the proportions of infants, that is, those who received palivizumab and those who did not.

The randomized, controlled, single-centre study conducted in Turkey by Tavsu was aimed at evaluating the hospitalization rate during the second RSV season among infants who were eligible for palivizumab during their first year of life. The participants were preterm infants of <32 weeks' GA who did not have a chronic lung disease, heart disease or another serious health problem. During the 2009-2010 RSV season, 83 infants were divided into two groups. One received palivizumab, while the other did not. During the subsequent season, the infants in both groups did not receive any immunoprophylaxis. The results of the study were as follows:

- During the first season, the hospitalization rate observed in the palivizumab group was nil but was 24.4% in the control group, for an odds ratio (OR) of 3.86 (95% CI: 1.47 to 10.13).
- The second-season results were not different.

The methodological quality of this study was considered good, and the groups were homogeneous in terms of the known parameters. The specificity and sensitivity of the screening test were high. The results clearly showed that palivizumab reduced the RSV hospitalization rate, for a substantial absolute difference of 24.4% between the two groups. Surprisingly, this result was reproduced during the second season, even though neither of the groups received palivizumab. Despite some of the study's limitations, INESSS feels that the size of the observed difference is sufficient to confirm the superiority of the effect of palivizumab.

In conclusion, few studies of acceptable quality have been published since the IMpact-RSV study, whose external validity has diminished. Nonetheless, the results of the latest studies do not contradict those of the IMpact-RSV study as regards cases of severe or extreme prematurity in infants with no medical risk factor other than prematurity, which indicates that palivizumab is more efficacious than placebo or no prophylaxis in preventing RSV hospitalizations in preterm infants of ≤32 weeks' GA. Consequently, INESSS feels that the therapeutic value of palivizumab has been demonstrated to its satisfaction with regard to the population of interest. Lastly, it considers that the data are presently insufficient to revise downward the cutoff GA for palivizumab eligibility.

D. Opinion of the members of the Advisory Committee on the Use of Palivizumab

According to the members of the Advisory Committee on the Use of Palivizumab, there have been significant advances in neonatology in the past few years, so much so that preterm infants are now healthier and present with less residual lung damage than before, whether or not they have bronchopulmonary dysplasia. However, they feel that preterm infants of <33 weeks' GA with no risk factor other than prematurity still constitute a group of infants considered at high risk for severe RSV infection. Furthermore, the methodological quality of the published studies is not good enough to justifying selecting, on the basis of the results, a GA group whose infants would be more likely to be at risk. Consequently, the experts feel that Criterion No. 1 should be renewed as is, based on the results of the IMpact-RSV study, even though its external validity has diminished over time.

E. INESSS's recommendation

Given the results of its analysis of the scientific data and the Advisory Committee's opinion, INESSS recommends maintaining Criterion No. 1, which is as follows:

- *Infants born at <33 weeks' gestation and <6 months of age at the start of the RSV season.*

4.1.2 Preterm infants with risk factors identified by Sampalis [2008]

A. Québec eligibility criteria

<table>
<tr><td>2014-2015 season</td><td>Criterion No. 2
Infants born at 33 to 35 $^{6/7}$ weeks' gestation and who are <6 months of age at the start of the RSV infection season and have a score >48 on the risk scale presented by Sampalis (2008).
<table>
<tr><th>Risk factor</th><th>Points</th></tr>
<tr><td>Low birth weight for his/her gestational age (<10th percentile) [1]</td><td>12</td></tr>
<tr><td>Male gender</td><td>11</td></tr>
<tr><td>Born in November, December or January</td><td>25</td></tr>
<tr><td>No history of eczema in the immediate family (mother, father, brothers or sisters)</td><td>12</td></tr>
<tr><td>Subject or siblings attending daycare</td><td>17</td></tr>
<tr><td>> 5 individuals in the household, including the subject</td><td>13</td></tr>
<tr><td>≥ 2 smokers in the household</td><td>10</td></tr>
<tr><td>Ref.: Sampalis JS et al. Development and Validation of a Risk Scoring Tool to Predict Respiratory Syncytial Virus Hospitalization in Premature Infants Born at 33 through 35 Completed Weeks of Gestation. Med Decis Making 2008; 28(4):471-480.</td><td>Total</td></tr>
</table>
[1]Based on the Canadian growth curve published by Kramer et al., 2001.</td></tr>
<tr><td>2015-2016 season</td><td>Criterion revoked.</td></tr>
</table>

B. Background

The evidence used to establish Criterion No. 2 (stated above) was from the IMpact-RSV study, which was described and evaluated earlier. The main results of interest concerning the category of preterm infants described above are as follows:

- The hospitalization rate among the infants who received palivizumab was 1.8% compared to 8.1% in those who received placebo, for a 78% reduction in the relative risk of hospitalization (95% CI: 66% to 90%; $p < 0.001$).
- The reduction in the relative risk of hospitalization in relation to the administration of placebo in the group of infants born at 32 to 35 weeks' GA was 80% ($p = 0.002$).

According to various sources, it is estimated that infants born at 33 to 35 weeks' GA account for approximately 5% of births. Because of the high number of cases eligible for palivizumab and the costs associated with its use, several researchers have attempted to determine the factors that predispose to a severe RSV respiratory tract infection that could require hospitalization. Such an approach would then enable one to target sufficiently at-risk infants to receive palivizumab. Therefore, to optimize resource utilization, INESSS used the validated tool presented by Sampalis for assessing the risk of hospitalization [2008] to select infants at moderate risk and high risk for hospitalization.

By way of information, it will be noted that the results of Notario's *post hoc* analysis, described and critiqued above, indicate that 2.2% (3/136) of the infants born at 33 to 35 weeks' GA who received

palivizumab were hospitalized compared to 8.2% (6/73) of those who received placebo, for a non-statistically significant relative risk reduction of 73.2% (95% CI: -10.8% to 96.4%).

In brief, the results of this analysis indicated that the absolute hospitalization rates observed in the subgroup of infants born at 33 to 35 weeks' GA were similar to those observed in the overall population in the IMpact-RSV study but did not demonstrate that palivizumab prophylaxis has superior efficacy. This conclusion is still uncertain, mainly because the IMpact-RSV study was not designed for performing subgroup analyses. Nonetheless, it is interesting to know the absolute hospitalization rates and to compare them to those observed in more recent studies.

In 2015, most of the members of the Advisory Committee on the Use of Palivizumab had proposed that palivizumab immunoprophylaxis no longer be offered to preterm infants who were eligible for it under Criterion No. 2 (stated above), provided that the MSSS put in place a structured follow-up process for these infants. Furthermore, in its preliminary report, INESSS had expressed reservations about immediately revoking the criterion in question for the 2015-2016 season because it wanted to continue analyzing the scientific literature.

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

These two organizations, the AAP and the CPS, no longer recommend palivizumab prophylaxis in children concerned by Criterion No. 2 (stated above).

INESSS's systematic review of the scientific literature [2016]

A number of publications identified report efficacy results for palivizumab in preterm infants. However, few of them provide information on its effect specifically in those born at 33 to 35 weeks' GA who do not have bronchopulmonary dysplasia or congenital heart disease, that is, the infants concerned by Criterion No. 2 (stated above). This is why studies that present results for infants born at 32 to 35 weeks' GA were examined as well, since they include the population concerned by the eligibility criterion to be reevaluated. Thus, the studies selected were those by Blanken [2013], Mitchell [2006] and Wegner [2004].

The MAKI study (Blanken) was a randomized, double-blind, phase III, multicentre trial conducted in Europe, more specifically, in the Netherlands, from April 2008 to December 2010. Its secondary objective was to compare the efficacy of palivizumab with that of placebo in preventing hospitalizations due to an RSV respiratory tract infection (RTI) (confirmed with a screening test) in 429 healthy preterm infants with a GA ranging from 33 to 35 weeks and a chronological age of <6 months at the start of the RSV season. The results indicate that 0.9% of the infants who received palivizumab during the RSV season were hospitalized compared to 5.1% of those who had not, for an absolute difference of 4.2% and an 82% reduction in the relative risk of hospitalization (95% CI: 18% to 157%; $p = 0.01$).

This study was considered to be of good methodological quality. It turns out, however, that the confidence interval mentioned above is wide, which is indicative of an imprecise result concerning the hospitalization rate, perhaps because this was a secondary outcome measure and because the sample

size had not been determined on the basis of it. Furthermore, INESSS found heterogeneity between the two groups in terms of their baseline characteristics, which does not seem to have been taken into account in the statistical analysis. This may have influenced the hospitalization rates. As well, the environmental factors that can influence the risk of severe infection were not documented, with the result that it cannot be determined if the two groups had the same level of risk. Nonetheless, INESSS recognizes that palivizumab is effective in preventing hospitalizations in the preterm infants of interest. However, a comparison of the hospitalization rates observed in the context of clinical practice in this study indicates that they were lower than those observed in the IMpact-RSV study, which suggests that size of the effect of palivizumab has diminished over time.

Mitchell's study [2006], a Canadian retrospective, observational cohort study, was aimed at assessing the impact using palivizumab on the number of hospitalizations due to a screening test-confirmed RSV RTI over a period covering six RSV seasons, using data from the charts of preterm infants born at <36 weeks' GA and residing in Calgary and Edmonton. A palivizumab immunoprophylaxis program based on AAP recommendations was introduced in 1999 in Calgary. However, such a program was not initiated in Edmonton until 2003. Preterm infants were divided into two groups, depending on whether they were considered to be at high or moderate risk for hospitalization. Preterm infants at high risk were those: 1) who were born at <33 weeks' GA or 2) who were born at 33 to 35 weeks' GA and were <6 months of age before the start of or during the RSV season and who had chronic lung disease of prematurity or were receiving home oxygen after their discharge from hospital. Infants at moderate risk were those born at 33 to 35 weeks' GA who had no medical risk factor other than prematurity and who were <6 months of age before or during the RSV season. The hospitalization rates were calculated for the "pre-palivizumab" period, which covered three RSV seasons (1995 to 1998) and for the "post-palivizumab" period, which covered three RSV seasons as well (1999 to 2002), during which the immunoprophylaxis program was in operation in Calgary, but not in Edmonton. The main results observed for the preterm infants at moderate risk for hospitalization in both cities were as follows:

- In Calgary, no statistically significant difference was observed between the hospitalization rates before and after the introduction of the immunoprophylaxis program: 3.3% versus 2.7%, respectively ($p = 0.389$).
- In Edmonton, the hospitalization rate decreased during the post-palivizumab period in relation to the pre-palivizumab period (2.1% versus 4.1%, respectively; $p = 0.021$), despite the fact that there was no immunoprophylaxis program in this city during the six RSV seasons covered by the study.
- The hospitalization rates from 1995 to 1998 were comparable in both cities, 3.3% in Calgary and 4.1% in Edmonton, even though no children received palivizumab prophylaxis.

This study was considered to be of good methodological quality. In fact, it consists of a population-based analysis of an evaluator-independent outcome measure. The results for Calgary indicate that the efficacy of palivizumab prophylaxis is superior to no immunoprophylaxis in preventing RSV hospitalizations. The hospitalization rates obtained in Edmonton were of the same order of magnitude as that obtained in Calgary in the group of infants who did not receive palivizumab. This suggests that there was no major difference in medical practice between the two cities or over time.

Wegner's study [2004], a retrospective, observational cohort study carried out in North Carolina, was aimed at evaluating, for the 2002-2003 RSV season, the direct costs associated with palivizumab

immunoprophylaxis and RSV treatment in preterm infants born at 32 to 35 weeks' GA who were <1 year of age compared to those who did not receive palivizumab. These infants could not have had any heart disease or chronic lung disease. However, they had to have at least 2 of the 4 risk factors that were part of the eligibility criteria in effect at the time for this group of preterm infants. The results did not show a difference (p = 0.0782) between the proportion of infants hospitalized for an RSV RTI who had received palivizumab (5/185, or 2.7%) and that of the infants who had not received it (12/182, or 6.6%). Furthermore, no difference between the groups was found with regard to the total number of days of hospitalization or the total number of intensive care unit days.

This study is considered to be of good methodological quality, based on the standards for evaluating observational studies. However, INESSS cannot disregard a major limitation that could affect the accuracy of the results, which is that some hospitalizations were recorded on the basis of the diagnoses in the database when the RSV screening test had not been performed. On the other hand, the sensitivity of the RSV screening test is approximately 80 to 90%. When evaluating this study, one must take into account the fact that the characteristics of RSV seasons vary over time and that the results concern only one season. Be that as it may, they suggest that palivizumab conferred little or no benefit in preventing hospitalizations in the group of preterm infants with risk factors in this study, although it is not known exactly if the risk of hospitalization was moderate or high.

Other publications

Since the magnitude of the hospitalization rates obtained in the controlled trials IMpact-RSV and MAKI differs, INESSS chose obtain data on changes in hospitalization rates from observational studies, focusing on those carried out in the United States and Canada. It identified those by Ambrose [2014 (REPORT)], Mitchell [2011 (CARESS)], Ryan [2016], Paes [2009] and Law [2004 (PICNIC)]. Furthermore, among the literature submitted by the manufacturer of palivizumab, the SENTINEL1 study by Anderson [2016], a grouped analysis by Anderson (manuscript under peer review) and the PONI study by Stranak [2016] received special attention.

Studies involving infants who received palivizumab

Paes's study [2009], a prospective, single-centre cohort study carried out in Ontario, involved 430 preterm infants born at 33 to 35 weeks' GA who were <6 months of age at the start of or during the 2005-2008 RSV seasons. They were divided into three groups according to their level of risk of hospitalization due to an RSV RTI, as determined with the instrument presented by Sampalis. Only the infants considered to be at moderate or high risk for severe infection received palivizumab. The results indicate that none of the infants who received palivizumab was hospitalized, while 1.45% (5/346) of those at low risk, who did not receive palivizumab, were hospitalized.

Although observational studies do not provide the best level of evidence, INESSS feels that the methodological quality of Paes's study is acceptable for this type of study. The results showed that palivizumab was effective in preventing RSV hospitalizations. However, since there was no control group, its effect cannot be compared with that of no immunoprophylaxis. The results are therefore not very useful for comparing, in a clinical practice context, the extent of the benefits of palivizumab between the two subgroups of infants who received it, in terms of their respective level of risk of hospitalization. In any event, it turns out that palivizumab totally prevented hospitalizations in the

groups that received it. Lastly, of the 430 infants in the total cohort, 5 were hospitalized, for a calculated hospitalization rate of 1.2%, which is numerically lower than the rate of 2.2% reported in the Notario's *post hoc* analysis for a similar population (8.2%).

The CARESS study, a pan-Canadian, prospective, observational study, was aimed at building a registry of infants recruited from October 2005 to May 2009 who had received at least one dose of palivizumab that could be used to perform comparative analyses of interest involving several outcome measures. To be eligible, infants had to have at least one of the following risk factors for a severe respiratory tract infection: prematurity (GA ≤35 weeks), bronchopulmonary dysplasia or chronic lung disease of the newborn, hemodynamically significant heart disease or any other recognized health problem, such as a congenital airway anomaly or a neuromuscular disorder. One of the primary outcome measures was the rate of hospitalizations due to a screening test-confirmed RSV RTI. The main results were as follows:

- Of the 5286 children in the registry at the time, 3741 (70.8 %) had prematurity as their only risk factor. Their RSV hospitalization rate was 1.12%, while that for the total population was 1.38%.
- The group of preterm infants was the one with the lowest hospitalization rate among the palivizumab recipients, that is, 1.12% compared to 1.31% in the infants with bronchopulmonary dysplasia or a chronic lung disease, to 1.99% in those with heart disease, and to 2.78% in the other infants ($p < 0.0005$).
- Of the 3741 preterm infants, 45.5% had been born at ≤28 weeks GA, 38.7% at 29 to 32 weeks' GA, and 15.7% at 33 to 35 weeks' GA. The RSV hospitalization rate observed in these three subgroups was similar (respectively, 1.34%, 1.25% and 0.2%; $p = 0.395$).

The CARESS registry is a valuable source of data, since it provides an overview of hospitalization rates based on an evaluation in a real-world context in Canada. Furthermore, the collected data were analyzed using various stratifications. INESSS feels that the quality of the study is good, considering the type of design that was used. The CARESS study has the advantage of having evaluated one of the factors often neglected, namely, therapeutic compliance, which can influence results. In this regard, no difference between the patients who were hospitalized and those who were not was reported. Furthermore, it is important to point out that approximately 81% of the RSV hospitalizations were the subject of a screening test for this virus, which is a substantial percentage. These elements help increase the reliability of the results, in light of which INESSS feels that the hospitalization rate among the preterm infants who received palivizumab was low. Although no difference was observed in terms of the hospitalization rate between the infants with a GA of 29 to 32 weeks and those with a GA of 33 to 35 weeks, no conclusion can be drawn with regard to the size of the relative difference in terms of the efficacy of palivizumab between these two groups in the absence of a comparison group. Despite the limitations of an ordinary comparison between two studies, it seems that the absolute hospitalization rate in the group of infants with a GA of 33 to 35 weeks observed in the CARESS study was lower than that obtained in the IMpact-RSV study and reported by Notario (0.2% vs. 2.2%).

Studies involving children who did not receive palivizumab

The PICNIC study, a prospective, multicentre, observational study, involved a Canadian cohort of 1832 preterm infants who were born at 32 to 35 weeks' GA and followed during the first RSV season (2001-

2002 or 2002-2003) in their first year of life and who did not receive palivizumab. The study was aimed, among other things, at developing an instrument for predicting the risk of a severe RSV RTI that could lead to hospitalization. The results indicate that 140 infants were hospitalized for a respiratory tract infection, but an RSV screening test was performed in only 69% of them (n = 96). Lastly, 66 of these 96 infants had a positive test result, which gives a rate of hospitalizations definitely associated with RSV of 3.6% (66/1832), all risk factors combined.

This study is considered to be of good methodological quality. Its main strengths are that it was prospective, that it was conducted in Canada in a large number of primary, secondary and tertiary care centres, and that it is more recent than the IMpact-RSV study [1998]. Furthermore, the primary outcome measure is well defined, and a well-designed statistical analysis had been planned. The decision to hospitalize an infant was made by physicians who were not involved in the study and who were not influenced by whether or not the infant was participating in the study. Lastly, data were collected rigorously. Although some of the data were gathered during an interview with the infant's parents or guardians, the interviews were held regularly, that is, every month during the infant's follow-up so that it could be checked if the risk factors at those times were different from those determined at the start of the study. One of its limitations was the short observation time of two RSV seasons, given that the characteristics of RSV seasons vary over time. Furthermore, 44 hospitalized children did not have an RSV screening test. Lastly, preterm infants were eligible for palivizumab at that time, and they were excluded from the study. Their number is not reported. However, they were probably considered to be at greater risk for severe RTIs than those who did not receive palivizumab. Consequently, the cohort may not have been completely representative of preterm infants of 33 to 35 weeks' GA. In short, this study has more positive aspects than negative ones. This is why the observed hospitalization rate (3.6%) can reasonably be considered reliable. It is lower than that reported in Notario's analysis for a similar population (8.2%).

The REPORT study was a U.S. prospective, observational study conducted during two RSV seasons, 2009-2010 and 2010-2011, in more than 35 states. Its objective was to determine the incidence of laboratory-documented RSV infections and the associated risk factors. The cohort consisted of preterm infants born at 32 to 35 weeks' GA during the months of May to February and who were $\leq$6 months of age at recruitment. Furthermore, they must not have had hemodynamically significant heart disease or chronic lung disease of prematurity or have received palivizumab or have been considered for receiving it. Data were collected from September to May. The main results were as follows:

- The total number of participants was 1646, and their chronological age and GA distribution for each month of recruitment was equitable. A complete follow-up was conducted in approximately 82% or 85% of the infants, depending on the RSV season. Only 13% of the subjects were eligible for palivizumab, based on the AAP criteria in effect at the time.
- Of the 1646 infants, 82 (5%) were hospitalized, but the charts of 38 (46%) of them did not contain the results of the RSV screening test, and 4 (5%) of them had not had the test. Therefore, that leaves 57 infants (3.5%) in whom an RSV infection was clearly confirmed, which translates into a hospitalization incidence rate of 7.7 per 100 infant-years (95% CI: 5.8 to 9.9) from September to May and 11.8 (95% CI: 8.9 to 15.4 from November to March.
- Of the hospitalized infants, 16% had an ICU stay, and 11% required respiratory assistance (mechanical ventilation).

This study has the advantage of having been carried out fairly recently and on a large scale. However, certain weaknesses should be noted because they may have contributed to underestimating the incidence of hospitalizations due to an RSV RTI.

- The screening test results for a large number of patients were not available.
- The cohort consisted mainly of patients who were not eligible for palivizumab, which suggests that they may have been at lower risk for severe infections.
- A considerable proportion of the infants were not followed for the entire duration of the study.
- Given the large number of participating centres, there may have been some disparities in the hospitalization criteria.

The hospitalization rate of 3.5% for a screening test-confirmed RSV RTI observed during the periods from September to May is lower than that obtained in Notario's analysis of infants of a similar GA who had not received palivizumab (10.1%). However, this comparison is biased because of the higher number of months of follow-up in the REPORT study, that is, 9 months compared to 5 in the IMpact-RSV study. Thus, a higher number of hospitalizations may have been recorded in the REPORT study. If all the hospitalizations for an RSV RTI that were not confirmed by a screening test were considered as such, the hospitalization rate would increase to 5%. It would nonetheless still be lower than the rate obtained in Notario's *post hoc* analysis of the IMpact-RSV study.

Ryan's study [2016], a retrospective study of a Nova Scotia cohort, was carried out using administrative databases. It involved 2811 preterm infants born at 32 to 35 weeks' GA from June 1, 1998 to June 30, 2008, followed for 10 RSV seasons and <12 months of age at the time of the first RSV hospitalization. They must not have had heart or lung disease or have received palivizumab. This study was aimed at determining whether a subgroup of these infants was at greater risk for hospitalization based on certain risk factors present at birth. The hospitalization rate for all 10 RSV seasons covered by the study was 3.1%. Furthermore, it was not possible, using the 17 potential risk factors analyzed, to create a predictive tool for distinguishing a subpopulation of infants at moderate risk for hospitalization from one at high risk.

In INESSS's opinion, this study has the limitations generally associated with observational studies whose data are from administrative databases. For instance, the determination of RSV hospitalizations that was based on the presence of an accurate diagnosis is a source of uncertainty in the accuracy of the results. Furthermore, an RSV screening test was not systematically performed, which may have had an impact on the objectivity of the diagnosis and, indirectly, on the hospitalization rate. However, the investigators adopted a cautious approach to reduce the risk of an incorrect assessment of RSV disease burden. A simple comparison of the hospitalization rate observed in this study and Notario's *post hoc* analysis concerning preterm infants of the same GA who did not receive immunoprophylaxis, that is, 3.1% compared to 10.1%, suggests that this rate decreased substantially over time. Although Ryan's study is of a lower level of evidence than the IMpact-RSV study, the size of the difference between the hospitalization rates reported in these studies is large enough to suggest a real decrease in the incidence of hospitalizations over the years.

A study by Anderson, which was submitted as a manuscript and which is under peer review, consists of a pooled analysis of seven prospective observational studies, six of which have been published,

conducted in different countries in the Northern Hemisphere between 2000 and 2014, including the Canadian study PICNIC. The objective of this study was to assess the burden associated with hospitalizations due to an RSV RTI in preterm infants of 32 to 35 weeks' GA. They had to have been born during an RSV season, not have any comorbidity factors and not have received palivizumab. The pooled results, which are specific to preterm infants born at 33 to 35 weeks' GA, indicate a hospitalization rate of approximately 3.4%, which is similar to what the results specific to each of the weeks of gestation 33, 34 and 35 indicate. It will be recalled that the rate reported in the PICNIC study (3.6 %) was similar as well.

When selecting the studies, the authors took several measures to reduce regional and local biases. Nonetheless, INESSS considers it highly likely that there were still differences between the settings, in particular, in terms of practice standards and the characteristics of the RSV seasons specific to each region or that varied according to the study period, and environmental factors considered significant risk factors for severe RSV infection. Despite this, there are no large numerical differences between the results taken from the studies selected for the purposes of Anderson's analysis concerning the parameters pertaining to the incidence of hospitalizations. Furthermore, the hospitalization rates reported by Anderson are lower than that, 8.2%, yielded by Notario's *post hoc* analysis concerning preterm infants born at 33 to 35 weeks' GA who had not received palivizumab.

The PONI study was a prospective, observational cohort study conducted in 23 temperate-zone countries in the northern hemisphere, only one of which was in the Americas, namely, Mexico. The aim of this study was to evaluate the risk factors and burden associated with hospitalizations due to RSV infections (laboratory-confirmed) both during the entire duration of the study, which was from October 1, 2013 to April 30, 2014, and during the RSV season, which is from October to April. The eligible population consisted of preterm infants who were born at 33 to 35 weeks' GA and who were $\leq$6 months of age on October 1, 2013 or who were born during the period from April 1, 2013 to February 28, 2014. Excluded were those who had bronchopulmonary dysplasia, another chronic lung disease, hemodynamically significant congenital heart disease and those who had received palivizumab or were likely to receive it. However, infants with another underlying health problem, including cystic fibrosis and Down syndrome, were eligible. The main results of interest were as follows:

- Of the 2390 participants, 127 were hospitalized for a respiratory tract infection during the RSV season. Of this number, only 46 had a positive RSV screening test result, which gives a calculated RSV hospitalization rate of 1.9%, or an incidence rate of 6.1 hospitalizations per 100 infant-years.
- A screening test was not performed in 32 of the infants hospitalized during the RSV season. According to INESSS's calculations, if, in the worst-case scenario, one test had been positive, the hospitalization rate in this group of infants would have been 3.3%.
- According to calculations performed by INESSS regarding the 64 RSV hospitalizations during the entire duration of the study, the proportion of infants hospitalized with a GA of 33, 34 or 35 weeks was, respectively, 1.3%, 3% and 3.2%.

INESSS considers the methodological quality of the PONI study good as regards its objective. Another positive feature is that it involved a cohort of infants whose GA meets the Québec palivizumab eligibility criteria in cases of mild to moderate prematurity with no medical risk factor other than

prematurity (2014-2015 RSV season). INESSS found this study to have certain limitations that could have diminished its external validity, namely:

- No U.S. or Canadian centres participated in the study.
- There are probably differences between the different countries in terms of clinical practice, environmental hospitalization risk factors, and the sensitivity of the screening tests used.

In any event, INESSS feels that the data reported in this study are of little use to it for assessing the impact of discontinuing palivizumab immunoprophylaxis in the infants concerned in the absence of a comparison group. At the very least, we note that, during the RSV season, the RSV hospitalization rate was much lower than that reported in Notario's *post hoc* analysis concerning a similar population. Furthermore, preterm infants born at 33 weeks' gestation were hospitalized at least 50 % less often than the others. This is only one assessment, which is not based on a statistical analysis.

SENTINEL1 was a multicentre, observational cohort study carried out in the United States after the new AAP guidelines came into effect [2014]. These guidelines no longer recommend the administration of palivizumab to preterm infants of 29 to 35 weeks' GA who have no medical risk factor for severe RSV infection other than prematurity. The objective of this study was to characterize hospitalizations due to RSV infections, nosocomial or otherwise, in this group of infants, particularly with regard to their GA, their chronological age and infection severity. As well, the infants had to be <12 months of age at the time of their admission to hospital for laboratory-confirmed RSV infection. The data were collected and processed prospectively and retrospectively. The planned observation periods in the protocol were the 2014-2015 and 2015-2016 RSV seasons. However, only the results for the first season are reported in the article. The main results were as follows:

- Of the 702 infants hospitalized with community-acquired RSV infection, 42% were admitted to an intensive care unit, and 20% of them required respiratory assistance (mechanical ventilation).
- The above-mentioned specialized care and respiratory assistance were required mainly by the preterm infants of 29 to 32 weeks' GA.
- The subgroups of infants of 29 to 32 and 33 to 34 weeks' GA were at greater risk for severe RSV infection than the subgroup of infants born at 35 weeks' GA in terms of the two outcome measures mentioned above.
- There was no statistically significant difference between the subgroup of infants of 29 to 32 weeks' GA and that of infants of 33 to 34 weeks' GA in terms of the two outcome measures mentioned above.
- In all the subgroups of interest, it was always the infants who were <3 months of age at the time of their hospitalization who were the most numerous with regard to the two outcome measures in question.

INESSS considers the methodological quality of the SENTINEL1 study good as regards its objective. A prospective follow-up based on the gathering of additional retrospective data increases the likelihood of identifying the entire population of interest. Nonetheless, INESSS feels that this study does not address its main concerns regarding the Québec eligibility criteria in effect during the 2014-2015 RSV season. In fact, this study cannot be used to assess the impact of no immunoprophylaxis on the incidence of RSV hospitalizations in a cohort of preterm infants born at 33 to 35 weeks' GA who would

have been eligible to receive palivizumab, since no comparison had been planned with a contemporary cohort (historical or otherwise) that was eligible and that actually received it. As well, none of the GA groups chosen for the purpose of presenting the study's results corresponds to the population of infants concerned by the Québec palivizumab eligibility Criterion No. 2 that was in effect during the 2014-2015 RSV season. Nonetheless, it is interesting to note that the results concerning the proportion of infants admitted to an intensive care unit or who were given respiratory assistance are similar in the infants in the 29-32 weeks' GA group and the 33-34 weeks' GA group. However, assessing these results in the absence of a control group is of little use for determining the actual size of the effect of palivizumab immunoprophylaxis for each of these subgroups for all the hospitalization-related outcomes. Lastly, the preponderance of hospitalizations in infants <3 months of age is consistent with what was previously observed in other studies.

In conclusion, INESSS notes that few studies of superior quality have been conducted since the publication of the IMpact-RSV study in 1998. The only new randomized controlled clinical trial [Blanken *et al.*, 2013], which was conducted during one RSV season in preterm infants of 33 to 35 weeks' GA, showed palivizumab to have superior efficacy to no prophylaxis in reducing the RSV hospitalization rate, that is, an absolute difference of 4.2% between the compared groups. The results for this outcome measure in the two controlled observational cohort studies [Mitchell *et al.*, 2006; Wegner *et al.*, 2004] did not reveal a statistically significant difference for the efficacy of palivizumab compared to no prophylaxis. Furthermore, the results of the observational studies examined revealed hospitalization rates ranging from 0 to 2.7% for the use of palivizumab prophylaxis and rates ranging from 1.9 to 6.6% for no prophylaxis, the latter rates mostly being less than or equal to 3.6%. Many of these studies had similar weaknesses, namely, RSV screening methods of varying sensitivity, a diagnosis determined from administrative databases with no systematic RSV screening test, and a too-short duration (small number of RSV seasons). Nonetheless, because of the similar results of several North American studies, it seems that RSV RTI hospitalization rates have probably decreased in the absence of palivizumab immunoprophylaxis since the publication of the IMpact-RSV study, in which the hospitalization rate for all the Canadian infants in the placebo group (14.7%) was, in addition, considerably higher than that for infants of other nationalities. It goes without saying that this observation has direct consequences on the size of the absolute difference between the hospitalization rates obtained for the infants who received palivizumab prophylaxis and those observed for no prophylaxis, which is reportedly now in the order of 2%. This indicates that palivizumab has a positive effect. Therefore, given the literature that was analyzed, without denying the efficacy of palivizumab in preventing severe RSV infections that can lead to hospitalization, INESSS is of the view that the size of the effect of palivizumab on the decrease in hospitalizations is now insufficient for recognizing its therapeutic value in preterm infants of 33 to 35 weeks' GA.

D. Opinion of the Advisory Committee on the Use of Palivizumab

According to certain members of the Advisory Committee on the Use of Palivizumab, major advances have been made in neonatology in the past few years, with the result that preterm infants are now healthier and have less residual lung damage than before, whether they have bronchopulmonary dysplasia or chronic lung disease of the newborn or not. Consequently, the experts feel that the external validity of the IMpact-RSV is therefore diminished. Several of them pointed out the fact that the environment has changed since this study and that its results cannot, by themselves, justify the merits of presently offering palivizumab to preterm infants of 33 to 35 weeks' GA. For instance, a

change was made to the practice standards regarding the percent saturation required to justify hospitalization. Previously, it had to be less than 95%, whereas it should now be less than 90%, a difference that has a significant downward effect on the number of hospitalizations. On the other hand, proportionately, hospitalized infants are more seriously ill than before.

In the opinion of the Committee's members, the proportion of infants hospitalized for RSV infection has decreased considerably in the past 20 years, a decrease that is very likely due to multiple factors. To support this observation, they invoke the results of some of the studies presented above (CARESS, PICNIC, Paes and Ryan). In their opinion, comparing absolute hospitalization rates provides a more accurate assessment of the size of the effect of palivizumab than the reduction in the relative risk of hospitalization, whose value can give the illusion of a greater effect. The value of the NNT can also be taken into account. That calculated from the results reported by Notario for preterm infants born at 33 to 35 weeks' GA is approximately 16. Considering the low hospitalization rates for infants who did not receive any immunoprophylaxis, which rates are from the studies by Ryan and Law (PICNIC), and a decrease in the risk of hospitalization for infants who received palivizumab prophylaxis, which can vary from 60 to 80%, the value of the NNT can vary from 35 to 69, which is a considerable increase. Based on studies conducted in real-world contexts, most of the experts consulted consider the extent of the estimated benefits of palivizumab insufficient for it to be continued to be administered to preterm infants of 33 to 35 weeks' GA who have no medical risk factor other than prematurity.

A minority of experts do not share this opinion because the level of evidence of the observational data is, in their opinion, too low to make such a decision. It turns out that in the best study (IMpact-RSV), the maximum reduction in the risk of hospitalization was observed in this very population. Furthermore, based on these experts' experience, these infants may be more severely ill if they contract RSV, given that they are born during the period when their pulmonary alveoli are starting to form. Indeed, this would put these infants at greater risk for seeing their condition worsen if they contract an RSV infection than those born at less than 33 weeks' gestation or those born at ≥36 weeks' gestation. However, if it turns out that the palivizumab is not efficacious in this group, selecting infants with a Sampalis risk scale score of 65 to 100, which indicates a high risk of hospitalization, would, perhaps, be an effective strategy if the result of Paes's [2009] were taken into account.

Observations during the 2015-2016 RSV season

Several of the experts consulted did not feel that there was a significant increase in the number of RSV hospitalizations during this period or that the infants with RSV infection were more severely ill, whether it was the overall pediatric population or, more specifically, preterm infants born at 33 to 35 weeks' GA, who ceased to being eligible for palivizumab immunoprophylaxis, as per the criteria established for this season. It seems that the virus that caused the most problems was the influenza type B virus. These experts pointed out that, according to the Institut national de santé publique du Québec (INSPQ), the last RSV season was not very intense.

The Committee's members deplored the fact that no objective, independent follow-up process had been put in place for this specific cohort, a measure that they had recommended in 2015 in the event that this cohort would cease to be eligible for palivizumab. They were of the view that it would be necessary to assess the impact of such a change over several years, given the potential differences in the characteristics of RSV seasons over time. On his own initiative, one of the experts consulted will

conduct a study at the hospital where he practices in order to examine the impact of discontinuing palivizumab immunoprophylaxis during the last winter season on the different outcome measures pertaining to RSV hospitalizations in the infants of interest. The results of this study will apparently be known in the fall of 2016. Despite this undertaking, which is worth mentioning, the experts reiterated the need for a structured follow-up process so that the data for all the Québec infants concerned will be collected and processed.

Possible options for the 2016-2017 RSV season

During discussions, INESSS submitted several options to be evaluated for the next season, based primarily on the results observed in certain subgroups of preterm infants in the different observational studies examined, namely:

1. To reintroduce the previous eligibility criterion No. 2 as is.
2. To make only high-risk (according to the Sampalis scale) preterm infants (33 to 35 weeks' GA) eligible.
3. To make preterm infants of 33 to 34 weeks' GA eligible (criterion determined on the basis of a similarity between infants born during the 35^{th} or 36^{th} week with regard to RSV hospitalizations).
4. To make preterm infants (of 33 to 35 weeks' GA) with a chronological age at the start of the RSV season of <3 months eligible.

From the standpoint of clinical relevance alone, the option of modifying the criteria to select one of these subgroups was not considered by the experts, most of whom recommend maintaining the revocation of Criterion No. 2. The main arguments provided were as follows:

- The scientific literature, recent or otherwise, is insufficient to justify modifying or reintroducing this criterion.
- It has never been shown that palivizumab has a preventive effect on the mortality associated with RSV infections.
- There is no available evidence on the effect of palivizumab on decreasing the longer-term complications associated with RSV infections, such as asthma.
- There is currently no data demonstrating that palivizumab would have prevented life-threatening complications in the infants in this cohort during the last RSV season. Current studies will, perhaps, provide answers in this regard.

E. INESSS's recommendation

Given the results of its analysis of the scientific data, the recommendations in the Canadian and American guidelines, and the Advisory Committee's majority opinion, INESSS is of the opinion that the revocation of Criterion No. 2 should be maintained for the next few RSV seasons. It reiterates the need to carry out structured, independent monitoring of changes in the health of the infants concerned by this recommendation.

4.1.3 Children with various illnesses that have a significant impact on respiratory function

4.1.4 Children with bronchopulmonary dysplasia or chronic lung disease of the newborn

A. Québec eligibility criteria

2014-2015 season	**Criterion No. 3** Children <24 months of age with: • a chronic lung disease; **or** • a medical condition with severe respiratory complications; **and** • who required oxygen during the 6 months preceding the RSV season; **or** • who require oxygen during the RSV season.
2015-2016 season	**Criterion No. 2** Children <24 months of age at the start of the RSV season who have chronic lung disease of the newborn (defined as the need for oxygen at 36 weeks' GA) or bronchopulmonary dysplasia (defined as the need for oxygen at 28 days of life and until at least 36 weeks' GA) **and:** • who required oxygen during the 6 months preceding the RSV season; or • who require oxygen during the RSV season.

B. Background

The evidence on which the first version of Criterion No. 3 (stated above) was based were from the IMpact-RSV study, which was presented above in Section 4.4.1 B. One of the study populations consisted of children <24 months of age with bronchopulmonary dysplasia requiring treatment (steroids, bronchodilators, diuretics or supplemental oxygen). The results showed that the efficacy of palivizumab was superior to that of placebo in reducing the RSV hospitalization rate. It was 7.9% in the infants who received palivizumab and 12.8% in those who received placebo, for a 39% reduction in the relative risk of hospitalization (95% CI: 20% to 58 %; p = 0.038).

The purpose of modifying Criterion No. 3, which had been in effect since June 2005 and which had been recommended in June 2006 by the Conseil du médicament, was to broaden its scope by adding health problems associated with severe respiratory complications, such as cystic fibrosis, neuromuscular disorders and respiratory tract anomalies, which, at the time, were the subject of nonconforming requests submitted for evaluation. The requirement of the need for oxygen therapy made it possible to target severely affected patients. Furthermore, the term "bronchopulmonary dysplasia" had been changed to "chronic lung disease". The decision that led to these additions was based more on expert opinion than on quality scientific data.

From the analysis of the cases involving nonconforming requests approved during the 2014-2015 season and the understanding of the Committee's experts, it emerged that the wording of Criterion No. 3 was open to interpretation. In fact, a large percentage of these cases involved children with cystic

fibrosis or a health problem that was causing airway secretion clearance problems, such as certain neuromuscular disorders or respiratory tract anomalies. Furthermore, in the mind of several of the Committee's members, this criterion mainly concerned children with parenchymal damage attributable to chronic lung disease of the newborn or to bronchopulmonary dysplasia. To better analyze the populations of children with different health problems that have harmful consequences on respiratory function and to thus reduce the ambiguity surrounding their eligibility criteria, a pragmatic approach involving an analysis by type of disease was recommended.

C. Scientific publications selected

Positions of the AAP [2014] and the CPS [Robinson et al.*, 2015]*

The AAP's recommendations are as follows:

- During the first year of life of preterm infants who have developed chronic lung disease of prematurity, defined as a gestational age <32 weeks and a requirement for >21% oxygen for at least the first 28 days after birth.
- During the second year of life of infants who meet the above definition of chronic lung disease of prematurity and whose condition requires treatment (chronic corticosteroid therapy, diuretic therapy or oxygen) during the 6 months preceding the start of the second RSV season.

The CPS's recommendations are as follows:

- During the first year of life of infants <12 months of age at the start of the RSV season who have chronic lung disease of prematurity (defined as the need for oxygen at 36 weeks' GA) and who have an ongoing need for diuretics, bronchodilators, steroids or supplemental oxygen.
- During the second year of life of children aged 12 months to <24 months before the start of the RSV season who have chronic lung disease of prematurity (defined as the need for oxygen at 36 weeks' GA), who are still on supplemental oxygen or who were weaned from it during the 3 months preceding the current RSV season.

INESSS's systematic review of the scientific literature [2016]

Apart from the IMpact-RSV study [1998], the results of which are reported above, the following studies were selected for the systematic review: Grimaldi [2004], Mitchell [2006] and Pedraz [2003].

Grimaldi's study [2004], a French prospective, observational study, was aimed at evaluating the efficacy of palivizumab in reducing RSV hospitalizations. The study population consisted of preterm infants of ≤32 weeks' GA who were <6 months of age at the start of the RSV season and who had a history of bronchopulmonary dysplasia, defined as a need for oxygen that had persisted for at least the first 28 days after birth. The study concerned three consecutive RSV seasons: 1999-2000, 2000-2001 and 2001-2002. Palivizumab administration started during the 2000-2001 season. An RSV screening test was routinely performed in the infants with bronchiolitis. The main results were as follows:

- In the preterm infants of ≤32 weeks' GA who had bronchopulmonary dysplasia, the hospitalization rate during the first of the three seasons in those who did not receive any immunoprophylaxis was

46.2 % (12/26) compared to, respectively, 11.8% (2/17) and 3.8% (1/26) during the following two seasons, during which palivizumab prophylaxis was administered. It will be noted that 1 of the 17 infants eligible for palivizumab during the second season and 3 of the 26 eligible infants during the third season did not receive it.

- In the preterm infants who did not have bronchopulmonary dysplasia and whose GA was 32 weeks or less, the hospitalization rate during the first of the three seasons was 11.5% compared to, respectively, 14.7% and 5% during the following two seasons ($p < 0.05$).

This study is considered to be of low methodological quality. One of the main limitations is the absence of predefined uniform criteria for justifying the hospitalization of an infant. Furthermore, the hospital pediatricians were directly involved in prospectively collecting and processing the clinical data on bronchiolitis, which may have constituted an additional source of bias. Nonetheless, certain positive aspects are to be noted, such as screening tests having been performed on a routine basis and the continued use of the same type of test in a given hospital during the five RSV seasons, which limited bias due to variations in RSV detection sensitivity. Furthermore, palivizumab was administered systematically to newborns before their discharge from hospital if they met the above-mentioned requirements, except in cases of parental refusal. This increased the chances of obtaining a complete cohort. The results indicated a high hospitalization rate in the absence of immunoprophylaxis, which suggests that severely preterm infants are at very high risk for severe RSV infection. However, the hospitalization rate obtained in this study appears to be higher than that observed in the comparable subgroup in the IMpact-RSV study. The same holds true with regard to the difference between the proportions of hospitalized infants who received palivizumab and those who did not. Lastly, it is noted that the hospitalization rate for preterm infants of $\leq$32 weeks' GA who did not receive palivizumab was much higher than that for the infants in the comparable subgroup that did not have dysplasia, which shows that this parenchymal damage constitutes a major risk factor for severe infections.

In the Canadian observational study of Mitchell [2006], presented and critiqued above in Section 4.1.2 C, one of the populations consisted of infants at high risk for RSV hospitalization. These infants were born at 33 to 35 weeks' GA and were <6 months of age before the start of or during the RSV season and had a chronic lung disease (bronchopulmonary dysplasia) or were receiving home oxygen after their discharge from hospital. The main results were as follows:

- In Calgary, the hospitalization rate before the palivizumab immunoprophylaxis program was introduced was higher than that observed after, that is, 7.3% versus 3% ($p = 0.003$).
- In Edmonton, the hospitalization rates during the pre-palivizumab and post-palivizumab periods were similar, that is, 5% and 7.1%, respectively, in the absence of an immunoprophylaxis program in this city during the six RSV seasons covered by the study.

In a real-life experimental context, palivizumab significantly reduced the hospitalization rate after the immunoprophylaxis program was introduced in Calgary. By way of information, in the absence of immunoprophylaxis, the hospitalization rate in preterm infants with a chronic lung disease or bronchopulmonary dysplasia was at least twice as high as that in preterm infants of 33 to 35 weeks' GA. This is consistent with the fact that these diseases are known to increase the risk of severe infections in infants who have them.

This study is considered to be of good methodological quality. In fact, it is a population-based analysis in which the primary outcome measure was evaluator-independent. The results observed in Calgary indicate that the effect of palivizumab prophylaxis was superior to no immunoprophylaxis in preventing RSV hospitalizations. Since the hospitalization rates obtained in Edmonton were of the same order of magnitude as that for the group of infants in Calgary who did not receive palivizumab, it can be assumed that the risk of differences in medical practice and of differences over time is rather small in these cities.

Pedraz's study [2003], which was carried out in Europe, sought to compare two cohorts of infants, one that received palivizumab prophylaxis and one that did not, in terms of the rate of hospitalizations due to a screening test-confirmed lower RSV RTI and in terms of these children's risk factors. The first cohort consisted of 1583 infants who had participated in the Carbonell-Estrany studies (2000 and 2001) and who had been followed for two RSV seasons, 1998-1999 and 1999-2000, before the introduction, in 1999, of an immunoprophylaxis program in Spain. The other cohort consisted of 1919 infants who had received palivizumab during the following two RSV seasons, 2000-2001 and 2000-2002. All the infants had to have a GA of ≤32 weeks, have (or not have) a chronic lung disease, defined as the need for oxygen at the 36th week of gestation, and be ≤6 months of age at the start of the RSV season. The results indicated that the hospitalization rate observed in the preterm infants with a chronic lung disease was higher in the absence of immunoprophylaxis than when palivizumab was administered, that is, 19.9% and 5.5%, respectively, an absolute difference of 14.4% ($p < 0,007$). It was in this subgroup of infants that the size of the difference was the greatest. By comparison, this difference was of the order of 7% in the subgroup of preterm infants born at ≤28 weeks' gestation who had or did not have a chronic lung disease and in the subgroup of infants of 29 to 32 weeks' GA who had or did not have a chronic lung disease.

The methodological quality of this study is very poor. Its main limitation is that it used the populations from two studies to create the cohort of infants who received palivizumab. Therefore, the cohorts and the interventions were not comparable, with the result that uncertainty persists with regard to the size of the effect of palivizumab.

Other publications

Chang's study [2010], a Korean retrospective, single-centre study, sought to evaluate the efficacy of palivizumab in preventing hospitalizations due to a screening test-confirmed RSV infection in two cohorts of preterm children born at ≤35 weeks' gestation who were at high risk for RSV infection and who had a chronic lung disease (or bronchopulmonary dysplasia), defined as the need for ≥21% oxygen for at least 28 days after birth. In the first cohort (n = 75), the children received palivizumab during the 2005-2009 RSV seasons, while in the other (n = 53), the children did not receive it during the 2004-2009 seasons. All the children had to be <24 months of age at the start of the RSV season and have been treated (bronchodilators, diuretics, oxygen or corticosteroids) during the 6 months preceding the season. Children with certain risk factors, namely, immunodepression, a major congenital anomaly, a hereditary metabolic disease, a neuromuscular disorder or hemodynamically significant heart disease, were excluded. The main results were as follows:

- In all, 12 children who did not receive immunoprophylaxis were hospitalized for RSV infection (22.6%), while only 3 of the children who received palivizumab were (4%), an absolute difference of 18.6% ($p < 0.001$).
- No difference was observed between the two groups with regard to the duration of hospital stay or the number of children intubated in an intensive care unit.
- Only 4 infants had to be administered palivizumab during two seasons.

The methodological quality of this study is considered acceptable for this type of study. Knowing that the characteristics of RSV seasons vary over time, the observation of each group during four seasons can contribute to diminishing the differences within a given group. The exclusion of children with other risk factors is a positive aspect to be noted. Furthermore, the practice standards were likely similar in both groups, since the study was conducted at a single centre. However, this had a negative effect on the study's external validity. One of the limitations identified is that the study was carried out in Korea, a setting different from Canada. The results indicated that the hospitalization rate obtained for the group of children in this study who received palivizumab prophylaxis was lower than that obtained in the IMpact-RSV study and in certain other observational studies. The hospitalizations that were necessary despite immunoprophylaxis occurred right before the scheduled date for the administration of a palivizumab dose, which suggests that, at that time, the drug's efficacy may not have been optimal. It should be noted that the compliance rate was high at 92.2%. Also, in the group of children who did not receive palivizumab, 5 of the 23 who were hospitalized for a respiratory problem did not undergo an RSV screening test, which may have contributed to underestimating the RSV hospitalization rate. If they had been tested and the results had been positive, the relative difference in hospitalization rates between the groups would have been higher, which would have indicated that palivizumab had a positive effect. Despite this study's potential sources of bias, it is unlikely that the difference between the hospitalization rates observed between the two groups could decrease to such a point that the positive effect of palivizumab would no longer be significant.

The primary objective of Boyce's retrospective study [2000] was to compare RSV hospitalization rates during the first year of life in different groups in a cohort of Tennessee children <3 years of age constructed during a 4-year period, from 1989 to 1993. The high-risk children were divided into four mutually exclusive groups according to the risk factor: preterm children, children with heart disease, children with bronchopulmonary dysplasia, and children with one of a set of health problems. All the other children were considered to be at low risk for hospitalization and constituted the control group for comparative purposes. Regardless of the chronological age group examined, the children with dysplasia always had the statistically highest hospitalization incidence rate ratio (at-risk group/low-risk group). It was 12.8 in the children <6 months of age, 14.3 in those aged 6 months to <12 months, and 20 in those aged 12 months to <24 months. As for the incidence rate ratios for the other three groups, stratified according to the children's chronological age, they never exceeded 5, with the exception of two of the 15 results of the comparisons that were performed. Although this study dates back a number of years and medical practice has evolved since, the incidence of hospitalizations per 1000 child-years (RSV seasons) among the children with bronchopulmonary dysplasia (1125, 428 and 146, according to whether they were aged 0 to <6 months, 6 months to <12 months, or 12 months to <24 months, respectively) differed considerably from that for the other three high-risk groups, who never exceeded 244.6, 12.9 and 60.1, respectively.

In the Canadian study CARESS, which is described in Section 4.1.2 C, the hospitalization rate for infants who received palivizumab and who had a chronic lung disease or bronchopulmonary dysplasia was 1.3%.

In conclusion, palivizumab's superior efficacy compared to no prophylaxis in reducing the incidence of RSV hospitalizations in preterm infants with bronchopulmonary dysplasia has been demonstrated. Although the level of evidence of the observational studies evaluated is lower than that of the IMpact-RSV study, it is seen that the results of the former do not contradict the superiority of palivizumab's efficacy demonstrated in the latter. Furthermore, preterm infants with bronchopulmonary dysplasia were at especially high risk for hospitalization compared to the other groups of infants in this study, given the hospitalization rates for these infants in the absence of immunoprophylaxis. In addition, the results of several of the studies analyzed suggest that the size of the effect of palivizumab is generally greater than that documented for other populations of at-risk infants. Consequently, INESSS feels that the therapeutic value of palivizumab is still recognized as immunoprophylaxis in the infants of interest.

D. Opinion of the members of the Advisory Committee on the Use of Palivizumab

In 2015, the experts consulted were of the opinion that eligibility Criterion No. 3 should be modified to include the definition of the population that it mainly concerned, the IMpact-RSV study subgroup consisting of children <24 months of age with bronchopulmonary dysplasia requiring treatment (steroids, bronchodilators, diuretics or supplemental oxygen). Even if the CPS now recommends administering palivizumab to these infants when they are <12 months of age instead, the experts consider that it would be too early to adopt this approach because the available scientific data are insufficient for justifying such a change. Although neonatology care and ventilation methods have improved significantly since the 1990s, this population of infants with lung damage still differs from other populations by the still-high risk of severe infection that can lead to hospitalization. The modification of Criterion No. 3 proposed by the experts for the 2015-2016 season was ratified by INESSS and subsequently by the MSSS. This criterion became Criterion No. 2, which was worded as follows:

- *Children <24 months of age at the start of the RSV season who have chronic lung disease of the newborn (defined as the need for oxygen at 36 weeks' GA) or bronchopulmonary dysplasia (defined as the need for oxygen at 28 days of life and until at least 36 weeks' GA) and:*
- *who required oxygen during the 6 months preceding the RSV season;*

  or
- *who require oxygen during the RSV season.*

In 2016, the experts are maintaining their position with regard to this population's eligibility. However, with last season's experience, certain adjustments to the criterion should be made to make the definitions in it easier to understand. The new wording would therefore be as follows:

- *Term or near-term children who are <24 months of age at the start of the RSV season and who have chronic lung disease of the newborn, defined as the need for oxygen at birth that has persisted because of chronic lung damage other than that mentioned in the other criteria;*

  or

- *Preterm children <24 months of age at the start of the RSV season who have bronchopulmonary dysplasia, defined as the need for oxygen shortly after birth and which persists up to at least 28 days of life and up to a gestational age of at least 36 weeks, this in the presence of a characteristic history of the disease;*

  and

- *Who had a persistent need for oxygen during the 6 months preceding the start of the RSV season or who require oxygen during the RSV season.*

E. INESSS's recommendation

In light of the literature evaluated and the opinion of the experts consulted, INESSS is of the opinion that the merits of administering, under certain conditions, palivizumab immunoprophylaxis to children with bronchopulmonary dysplasia and chronic lung disease of the newborn have been clearly demonstrated scientifically and clinically. To clearly understand the difference between these two types of damage and to make it easier to interpret the criterion that concerns them, INESSS fully recommends the changes to Criterion No. 2 proposed above by the members of the expert committee. Its wording would therefore be as follows:

- *Term or near-term children who are <24 months of age at the start of the RSV season and who have chronic lung disease of the newborn, defined as the need for oxygen at birth that has persisted because of chronic lung damage other than that mentioned in the other criteria;*

  or

- *Children <24 months of age at the start of the RSV season who have bronchopulmonary dysplasia, defined as the need for oxygen shortly after birth and which persists up to at least 28 days of life and up to a gestational age of at least 36 weeks, this in the presence of a characteristic history of the disease;*

  and

- *Who had a persistent need for oxygen during the 6 months preceding the start of the RSV season or who require oxygen during the RSV season.*

4.1.5 Children with cystic fibrosis

A. Québec eligibility criteria

2014-2015 season	**Certain cases authorized upon a nonconforming request or in accordance with the following Criterion No. 3:** Children <24 months of age with: • a chronic lung disease; **or** • a medical condition with severe respiratory complications; **and** • who required oxygen during the 6 months preceding the RSV season; **or** • who require oxygen during the RSV season.
2015-2016 season	**Criterion No. 3** Children <24 months of age at the start of the RSV season with cystic fibrosis who present with significant respiratory symptoms or failure to thrive.

B. Background

After the modification of Criterion No. 3 in June 2006, which made children with a chronic lung disease, such as cystic fibrosis, eligible, pediatric respirologists made representations to the effect that making the need for oxygen a systematic requirement deprived certain children considered to be at high risk for hospitalization from the benefits that this type of prophylaxis would have provided them. Since then, a number of children with cystic fibrosis have had access to palivizumab after the evaluation of nonconforming requests. It will be noted that INESSS's analysis of some of these cases revealed that these children had risk factors in addition to the disease itself. It will also be noted that the eligibility criteria in the current palivizumab immunoprophylaxis programs in certain provinces (see Appendix III to this report) include children with cystic fibrosis, this with no restriction other than age, which must be <12 months or 24 months, depending on the program.

For the 2015-2016 season, the MSSS ratified the addition of the eligibility criterion concerning children with cystic fibrosis, i.e., Criterion No. 3, proposed by INESSS in August 2015 in its preliminary report, subject to the need to continue its analysis.

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

According to the AAP, palivizumab should not be administered routinely to children with cystic fibrosis. This type of prophylaxis may, however, be considered in the following cases:

- During the first year of life of an infant with cystic fibrosis with clinical evidence of chronic lung disease or failure to thrive.
- During the second year of life of a child with cystic fibrosis who received palivizumab during his/her first year of life, if he/she has signs of a serious health problem (hospitalization due to an

exacerbation of lung damage during the first year of life or an abnormality on chest radiography or computed tomography that persists when the disease is stable) or if he/she presents with failure to thrive ($\leq 10^{th}$ percentile).

According to the CPS, palivizumab should not be administered routinely to children with cystic fibrosis. This prophylaxis may, however, be considered in the following cases:

- Children <24 months of age with cystic fibrosis, only if they are on home oxygen, have had a prolonged hospitalization for severe pulmonary disease or are severely immunocompromised.

INESSS's systematic review of the scientific literature [2016]

The retrospective, observational cohort studies of Giebels [2008] and Winterstein [2013] are the most relevant of the publications identified.

The objective of Giebels' study [2008], a single-centre study in Québec, was to evaluate the effect of palivizumab on hospitalizations for acute respiratory illness during the first RSV season following a diagnosis of cystic fibrosis from 1997 to 2005 in 75 children <18 months of age. For comparative purposes, two cohorts were formed using medical record data, according to whether or not the children had or had not received palivizumab. No difference between the groups in terms of the hospitalization rate for an acute respiratory problem or the mean duration of hospital stay was found. It will be noted that the RSV screening test was not performed in 3 of the 10 children who were hospitalized.

This was a case-control-type analysis of a chronological series considered to be of poor methodological quality. The outcome was not systematically measured, and *ad hoc* decisions were made regarding patient classification. This study seems to have been carried out *ad hoc* specifically for descriptive purposes, but the data were not handled in accordance with a rigorous protocol. Since the number of patients and events in each group was very small, a lack of statistical power could explain why there was no difference between the groups, not to mention that this study's major limitations greatly diminish the robustness of the results.

The objective of Winterstein's study [2013] was to evaluate the efficacy of palivizumab during RSV seasons in children with cystic fibrosis <24 months of age in a cohort of children, selected from administrative databases, who had received medical care in 27 American states from 1999 to 2006. When the cohort was established, a ratio of 1 palivizumab recipient (n = 575) to 4 nonrecipients, randomly selected (n = 2300), was respected for each index month. The primary outcome was that the number of RSV hospitalizations designated by means of diagnostic codes for the presence of RSV. The main results were as follows:

- The cohort of palivizumab recipients had certain associated health problems at a higher proportion than that observed for the nonrecipients, such as bronchopulmonary dysplasia, delayed growth and a history of oxygen therapy.
- No statistically significant difference was observed between the two cohorts in terms of the adjusted RSV hospitalization incidence rates, which were 2.4/1000 RSV season months (95% CI: 0.8 to 6.6) among the palivizumab recipients compared to 4.1/1000 RSV season months (95% CI: 2.8 to 6) among the nonrecipients, for a hazard ratio (HR) of 0.57 (95% CI: 0.2 to 1.6).

The methodological quality of the study is considered good. This independent study was funded by the Food and Drug Administration (FDA) and was carried out using objective data. Furthermore, the authors took many precautions, by observing a large number of rules, to obtain the most homogeneous groups possible and to select the most reliable data possible in order to reduce the sources of bias that could affect the results. A complex analysis took into account the changes in conditions over time. Furthermore, the statistical analysis took into account several potentially confounding variables. As well, the use of propensity scores and the performance of a sensitivity analysis to exclude the most severely ill patients, who were therefore more likely to be selected to receive palivizumab, are some of the positive aspects to be noted. Despite a much higher number of patients than that in other studies involving children with cystic fibrosis, the superiority of the effect of palivizumab has still not been demonstrated in relation to no prophylaxis in this population. The sensitivity analysis did not lead to a different conclusion. It will be noted that the number of hospitalizations reported was small, despite a relatively long observation period. This number was, perhaps, underestimated because event detection was based on a diagnostic code and because an RSV screening test was not always performed. These factors may have made it more difficult to demonstrate a difference between the groups.

Other publications

INESSS identified one recent study [Groves *et al*., 2016] that was not included in the systematic review.

The primary objective of Groves's study [2016], an Irish, single-centre, retrospective, observational cohort study, was to compare the number of hospitalizations attributable to RSV infection and their duration before (1997-2002) and after (2002-2007) the introduction of a palivizumab immunoprophylaxis program for infants with cystic fibrosis diagnosed during the neonatal period. Starting in 2002, these infants were eligible to receive palivizumab during the RSV season during their first year of life, regardless of their age, and during the RSV season in their second year of life, if they were considered to be at high risk or were <12 months of age. The main results of this study were as follows:

- All the infants in the palivizumab group (n = 45) received the drug during their first year of life.
- The rate of hospitalizations due to a screening test-confirmed RSV infection was 4.4% (2/45) in the group of palivizumab recipients and 21.3% (10/47) in the nonrecipient group, for a relative risk (RR) of 4.78 (95% CI: 1.1 to 20.7; p = 0.027).
- The median duration of hospital stay was shorter when palivizumab was administered: 3 days compared to 10 days (no supporting statistical analysis).

This study is considered to be of "poor" to "average" methodological quality. It does have the advantage of having been carried out at a regional hospital where the same type of RSV screening test was performed systematically. Although clinical practice may have changed during the 10 years of observation, the follow-up was uniform, since it was centralized at a single facility specializing in the treatment of this disease. Nonetheless, it is still possible that the sense of security associated with immunoprophylaxis may have influenced the criteria for deciding whether or not to hospitalize an infant. Furthermore, since a single hospital was involved, the study's external validity is diminished. As in all the above-mentioned studies, the influence of environmental risk factors, which are potential confounding variables, was not assessed. In addition, the substantial difference in the proportion of

male infants in the groups' baseline characteristics is a concern. It does not seem to have been taken into account in the statistical analysis. The results indicate that palivizumab helped reduce the RSV hospitalization rate after the introduction of immunoprophylaxis, with an absolute difference of 16.1% in relation to the previous period. Furthermore, these results suggest that palivizumab conferred benefits in terms of the duration of hospital stay. The 16.1% difference is considerable, but its accuracy is questionable, given the study's limitations. However, it would be very unlikely that the actual difference is nil. Although INESSS does not conclude beyond any doubt that palivizumab has superior efficacy, it does believe that there is probably a strong tendency in this direction.

In conclusion, INESSS notes that all but one of the studies that have attempted to demonstrate additional benefits of palivizumab prophylaxis compared to no immunoprophylaxis in children with cystic fibrosis have failed to do so. Most of these studies have, however, several limitations. To rule out doubt regarding the potential benefits of palivizumab in the population of interest, Robinson [2014] determined that, to conduct a good randomized, controlled trial whose results could show that palivizumab leads to a 50% decrease in the RSV hospitalization rate with a power of 80% and a type I error set at 0.05%, one would have to recruit 644 to 4777 children per group. This is a near-unrealistic objective, given the large number of patients that would be required and the fact that the prevalence of cystic fibrosis is not high. Consequently, INESSS is not able to comment on the therapeutic value of palivizumab in children with cystic fibrosis from an evidenced-based medicine perspective.

D. Opinion of the members of the Advisory Committee on the Use of Palivizumab

According to the experts consulted, the level of evidence of the scientific literature brought to their attention is too low for them to draw any conclusions from it. However, the relevance of administering palivizumab is justified from a clinical standpoint. In their opinion, RSV RTIs can have long-term harmful sequelae. They increase the risk of pulmonary scarring, of respiratory function deterioration and of shortening the time to a lung transplant, if applicable. There are few scientific data documenting these complications. Just as it is difficult to demonstrate the decrease in hospitalizations attributable to palivizumab immunoprophylaxis, it is difficult to use studies to assess the harm caused by RSV RTIs because of the small number of patients affected. For instance, only 20 to 30 new cases of cystic fibrosis in children are reported in Québec. One must also consider the fact that complications can occur over decades and that, additionally, it would be difficult to link them specifically to RSV infection because any severe respiratory tract infection can have such consequences. This is why treating physicians take every measure to prevent severe respiratory tract infections of any cause in children with cystic fibrosis considered to be at high risk for contracting them, including, in particular, systematic annual influenza vaccination.

Unlike the CPS, the experts are of the opinion that to be eligible for palivizumab, Québec children with cystic fibrosis should not necessarily have to meet the following requirements: the need for home oxygen, having had a prolonged hospitalization for severe lung disease or be severely immunocompromised. Contrary to the practice in the other Canadian provinces, no neonatal cystic fibrosis screening test is systematically performed in Québec. In Québec, children <24 months of age diagnosed with cystic fibrosis have therefore developed respiratory or gastrointestinal function symptoms. Therefore, from a clinical standpoint, the fact that these children have been diagnosed with cystic fibrosis at a young age is an indicator of disease severity and of the higher risk of contracting severe RSV infection.

As to whether palivizumab should be administered during the first year of life only or during the first 2 years of life, current practice is to prescribe this drug in all infants <12 months of age at the start of the RSV season. However, for those aged 12 months to <24 months, the physician assesses the need on the basis of the condition of the child, for whom a regular follow-up is done at one of the seven multidisciplinary clinics specialized in treating cystic fibrosis. Therefore, there is self-regulation in the application of this criterion. This is why the maximum age of eligibility should be less than 24 months.

In short, the position of the Committee's members is the same as that expressed in 2015. Therefore, the use of palivizumab is still considered clinically relevant for protecting children with cystic fibrosis who are <24 months of age at the start of the RSV season and who have significant respiratory symptoms or failure to thrive.

E. INESSS's recommendation

Given that it is very unlikely that a randomized, controlled trial of good methodological quality will be conducted to evaluate the benefits of palivizumab immunoprophylaxis in children with cystic fibrosis, INESSS believes that the opinion of the experts consulted should be used to determine the optimal conditions for using palivizumab in this population. These conditions have been determined in order to carefully select children considered to be at high risk for hospitalization due to a severe RSV RTI. Consequently, INESSS recommends, for the next RSV season, that Criterion No. 3, which reads as follows, be maintained:

- *Children <24 months of age at the start of the RSV season with cystic fibrosis who present with significant respiratory symptoms or failure to thrive.*

4.1.6 Children with neuromuscular disorders

A. Québec eligibility criteria

2014-2015 season	Certain cases authorized upon a nonconforming request.
2015-2016 season	**Criterion No. 4** Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of a neuromuscular disorder.

B. Background

The analysis of the cases in which nonconforming requests were approved during the 2014-2015 RSV season revealed that several requests concerning children with certain neuromuscular disorders whose manifestations can predispose to an exacerbation of an RSV respiratory tract infection had been approved for the following reasons: reduced ability to clear airway secretions because of ineffective cough, respiratory muscle weakness, a strong prevalence of gastroesophageal reflux, and a swallowing dysfunction increasing the risk of aspiration. This observation warranted an in-depth analysis of the relevance of including or not including a specific eligibility criterion for children with neurological disorders. It will be noted that the immunoprophylaxis programs in certain Canadian provinces (see Appendix III) cover this population, under certain conditions.

For the 2015-2016 season, the MSSS had ratified the addition of the eligibility criterion for children with neuromuscular disorders (Criterion No. 4) proposed by INESSS in August 2015 in its preliminary report, but subject to the need to continue its analysis.

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

According to the AAP, palivizumab may be administered during the first year of life of infants with a neuromuscular disease whose manifestations reduce the ability to clear upper airway secretions because of ineffective cough, since it is known that they are at risk for a prolonged hospitalization in the event of a severe lower respiratory tract infection.

According to the CPS, palivizumab should not be administered routinely to children with an upper airway obstruction. However, this drug may be considered to protect children <24 months of age who are on home oxygen, who are severely immunocompromised or who required a prolonged hospitalization for severe pulmonary disease.

INESSS's systematic review of the scientific literature [2016]

No publications concerning this population were identified.

Other publications

Given the absence of studies on the use of palivizumab in the population of interest, INESSS chose to obtain data on the risk of hospitalization due to an RSV RTI compared to the risk in children in other populations known to be at high risk. The studies by Zachariah [2011] and Kristensen [2012] were selected.

The objective of Zachariah's study [2011], a retrospective, observational cohort study, was to assess the risk of hospitalization due to an RSV lower respiratory tract infection and infection severity in hospitalized children with congenital malformations. The data were from Colorado administrative databases. Thus, two similar cohorts of children were established according to whether or not they had a congenital malformation. There were various types of morphological abnormalities: neurological, urinary, respiratory, orofacial and gastrointestinal. The children who also had any of the following risk factors were not included in the cohorts: chronic pulmonary disease, heart disease, pulmonary hypertension, prematurity, neurological disorder or an immune deficiency.

This study had the usual methodological limitations associated with the type of design that was used. The exclusion of children with other known risk factors that increase the risk of hospitalization is a positive aspect to be noted. The ratio of the hospitalization incidence rate for the children with spina bifida to the rate for those without spina bifida indicated a statistically higher risk attributable to this type of abnormality.

Kristensen's study [2012], a retrospective, observational cohort study, aimed to assess the risk of RSV hospitalization (1997-2003) and RSV infection severity in children <24 months of age with different

chronic health problems compared to that in healthy children of the same age. The types of problems, congenital and acquired, were diverse: chromosomal abnormalities, metabolic diseases, cardiac, gastrointestinal and respiratory tract malformations, neurological disorders, etc. In terms of results, the ratio of the hospitalization incidence rate in children with a neuromuscular disorder to the rate in children without a neuromuscular disorder indicated a statistically higher risk in the presence of the following problems in particular: cerebral palsy, muscular dystrophy and spina bifida. However, no additional risk of hospitalization was found for certain nervous system malformations or certain neuromuscular disorders, such as spinal muscular dystrophy, a congenital muscle tone disorder and congenital myasthenia.

This study had the limitations generally associated with a design that uses registry data, whose reliability may be compromised. However, certain positive aspects are worth mentioning, such as the following:

- The data gathered on 391,383 children under the age of 24 months were analyzed.
- A hospitalization was included if a positive RSV screening test result had been reported, although the test used was not the most sensitive one.
- Hospitalizations due to a nosocomial infection were excluded from the analysis of the duration of hospital stay so as not to overestimate it.
- Cross-checking the different databases revealed that 96% of the cases of RSV hospitalization were present in two registries, one of which was specifically for RSV.
- Several confounding factors were taken into account in the multivariate statistical analysis.

Given the foregoing, it emerges that certain neuromuscular disorders predispose to severe RSV infections that can lead to hospitalization.

In conclusion, the results of the above-mentioned studies suggest that certain neurological and neuromuscular disorders are independent risk factors for hospitalization due to severe RSV infection. It will be noted that certain results are consistent from study to study. As well, given the absence of studies evaluating the efficacy of palivizumab in children with a neuromuscular disorder, INESSS is not able to give an assessment of its therapeutic value in this population.

D. Opinion of the members of the Advisory Committee on the Use of Palivizumab

In the opinion of the experts consulted, the level of evidence of the studies concerning children with neuromuscular diseases is low. However, based on these experts' clinical experience, the risk of severe RSV respiratory tract infections is clearly higher in the presence of a neuromuscular disorder that causes muscle weakness to the point of significantly impairing the clearance of airway secretions, by reducing lung capacity and the ability to cough. This is why, in 2015, the experts felt that administering palivizumab to children who meet the following description was clinically indicated:

- *Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of a neuromuscular disorder.*

Given the absence of new data in 2016, the experts propose that Criterion No. 4 above, which was in effect during the last RSV season, be renewed. However, they now believe that it is necessary that the diagnosis of neuromuscular disorder be indicated by the treating physician on the palivizumab eligibility request form.

E. INESSS's recommendation

Given that it is very unlikely that a randomized, controlled trial of good methodological quality will be conducted to evaluate the benefits of palivizumab immunoprophylaxis in children with neuromuscular disorders, INESSS believes that the opinion of the experts consulted should be accepted with regard to the relevance of administering palivizumab to these children in certain cases. Therefore, INESSS recommends that Criterion No. 4 be maintained. Since this criterion is new, INESSS feels that it is important that the MSSS have a means of collecting data for analyzing the neuromuscular disorders of children for whom requests for palivizumab are made using the general form rather than the specific form for nonconforming cases, which was commonly done in the past. This is why the physician must indicate the diagnosis on the form. Therefore, the criterion would read as follows:

- *Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of a neuromuscular disorder. The diagnosis must be indicated on the request.*

4.1.7 Children with congenital anomalies of the upper respiratory tract

A. Québec eligibility criteria

2014-2015 season	Certain cases authorized upon a nonconforming request.
2015-2016 season	**Criterion No. 5** Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of congenital anomalies of the upper respiratory tract.

B. Background

The analysis of the nonconforming cases during the 2014-2015 RSV season revealed that several requests had been approved for children with a congenital anomaly causing impaired airway secretion clearance, such as choanal atresia, esophageal atresia with a tracheoesophageal fistula or various craniofacial malformations often associated with a genetic disease. This finding warranted an in-depth analysis of the relevance of including or not including a specific eligibility criterion for these children. It will be noted that the immunoprophylaxis programs in certain Canadian provinces (see Appendix III) cover this population, under different conditions.

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

According to the AAP, palivizumab may be administered during the first year of life of infants with a congenital anomaly that reduces the ability to clear upper airway secretions because of ineffective cough, since it is known that they are at risk for a prolonged hospitalization in the event of a severe lower respiratory tract infection.

According to the CPS, palivizumab should not be administered routinely to children with an upper airway obstruction. However, the administration of this drug may be considered in children <24 months of age who are on home oxygen, who are severely immunocompromised or who have required a prolonged hospitalization for severe pulmonary disease.

INESSS's systematic review of the scientific literature [2016]

No publication concerning this population was identified.

Other publications

Given the absence of studies on the use of palivizumab in the population of interest, INESSS chose to obtain data on the risk of hospitalization due to an RSV respiratory tract infection in these children compared to that in other populations considered to be at high risk. The studies by Zachariah [2011] and Kristensen [2012], which were presented and analyzed in Section 4.1.6 C, were selected. The populations included in these studies consisted of children with certain congenital airway anomalies, among others.

The main results of Zachariah's study concerning airway abnormalities were as follows:

- Children who had pulmonary dysplasia, hypoplasia or agenesis or who had palatoschisis (a congenital fissure in the palate) were hospitalized more frequently than those who did not.
- Having choanal atresia or a diaphragmatic anomaly did not increase the risk of hospitalization.
- The mean duration of hospital stay, the number of infections with a high severity score, and the proportion of children who required respiratory assistance were statistically higher in those who had pulmonary dysplasia, hypoplasia or agenesis or who had palatoschisis or choanal atresia than in those who did not.

The results show that certain respiratory tract anomalies had an upward effect on the rate of hospitalizations due to an RSV respiratory tract infection and on infection severity assessed with different parameters. Although the incidence of hospitalizations in the children with choanal atresia did not differ from that in the control group, these children were more severely ill if the other parameters studied are taken into consideration.

In Kristensen's study, the ratio of the hospitalization incidence rate in the children with a health problem to that in the healthy children showed a statistically higher risk of hospitalization in the presence of the following problems, among others: laryngeal or pulmonary malformations,

palatoschisis, cystic fibrosis, esophageal atresia, bronchopulmonary dysplasia, pulmonary interstitial syndrome, heart disease, Down syndrome and other chromosomal diseases, and metabolic diseases.

In conclusion, the results of the small number of published studies involving children with various chronic health problems or with a congenital abnormality suggest that some of these conditions constitute independent risk factors for hospitalization due to severe RSV infection. Because of these studies' low level of evidence, there remains some uncertainty regarding their conclusions. Nevertheless, certain results are consistent from study to study. As well, since there are no studies evaluating the efficacy of palivizumab in these children, INESSS is not able to give an assessment of the therapeutic value of palivizumab immunoprophylaxis in this population.

D. Opinion of the members of the Advisory Committee on the Use of Palivizumab

In the opinion of the experts consulted, the level of evidence of the studies involving children with a congenital anomaly is low. However, based on these experts' clinical experience, the presence of certain respiratory tract anomalies prevents efficient secretion clearance in some children, with the result that respiratory illness due to RSV can become complicated and quickly develop into a severe infection requiring hospitalization.

In 2015, the Committee's members were unanimously of the opinion that palivizumab should be administered to children with certain types of upper respiratory tract anomalies. However, one should carefully select the children at greatest risk. Therefore, only those <24 months of age whose anomaly significantly impairs secretion clearance should receive palivizumab immunoprophylaxis. The age limit chosen is that recommended in the IMpact-RSV study in cases of bronchopulmonary dysplasia. In 2016, the Committee's members are still of the same opinion and propose that Criterion No. 5, which was in effect during the last RSV season, be maintained. However, they are now of the opinion that it is necessary for the treating physician to indicate the diagnosis concerning the anomaly on the palivizumab request form.

E. INESSS's recommendation

The level of evidence of the available scientific data documenting the relative risk of RSV hospitalization in children with an airway anomaly is low. However, the two studies examined revealed that some of these anomalies are associated with a higher risk. Furthermore, the experts consulted confirmed this observation in their practice. As well, it is unlikely that a good-quality study to evaluate the efficacy of palivizumab in this specific patient population will be carried out because of the small number of children concerned. For all these reasons, and like these experts, INESSS is of the opinion that it is reasonable to offer palivizumab immunoprophylaxis to these children and recommends maintaining Criterion No. 5 for the next RSV season. Since this criterion is new, INESSS feels that it is important that the MSSS have a means of collecting data for analyzing the health of children for whom a request for palivizumab is made using the general form rather than the specific form for nonconforming cases, which was commonly done in the past. This is why the physician must indicate the diagnosis on the form. Therefore, the criterion would be worded as follows, and the form should be modified accordingly:

- *Children <24 months of age at the start of the RSV season in whom the clearance of airway secretions is significantly impaired because of a congenital anomaly of the upper airways. The diagnosis must be indicated on the request.*

4.1.8 Children with heart disease

A. Québec eligibility criteria

2014-2015 season	**Criterion No. 4** Children <24 months of age with hemodynamically significant congenital heart disease.
2015-2016 season	**Criterion No. 6** Infants <12 months of age at the start of the RSV season with hemodynamically significant congenital heart disease, cardiomyopathy or myocarditis or with moderate to severe pulmonary hypertension (the request must be submitted by a pediatric cardiologist to ensure the accuracy of the diagnosis).

B. Background

The evidence on which Criterion No. 4 (stated above) was based were from Feltes's randomized, double-blind, multicentre study [2003], which was aimed at comparing the efficacy of palivizumab to that of placebo in reducing the incidence of RSV hospitalizations during four consecutive RSV seasons (1998 to 2002). The population consisted of children <24 months of age with hemodynamically significant congenital heart disease that had not been operated or that had been partially corrected. The main results of this study are presented in the following table:

Results of Feltes's study [2003]

Population	**Hospitalization Rate**	
	Palivizumab	**Placebo**
Total population	5.5%	9.7%
	Reduction in relative risk 45% (95% CI: 23% to 67%; p = 0.003)	
Infants <6 months of age	6%	12.2%
Children 12 to 24 months of age	1.8%	4.3%
Canadian participants	7.6%	11.9%

For the 2015-2016 season, the MSSS had ratified the modifications to Criterion No. 4 proposed by INESSS in its preliminary report in August 2015.

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

The CPS [Robinson *et al*., 2015] now recommends palivizumab immunoprophylaxis in infants <12 months of age at the start of the RSV season with hemodynamically significant congenital heart disease. The AAP [2014] makes the same recommendation and adds the following specifications:

- Infants with acyanotic heart disease who are on medication to control congestive heart failure and who will require cardiac surgery;
- Infants with moderate to severe pulmonary hypertension.

INESSS's systematic review of the scientific literature [2016]

Only two studies were selected for the systematic review, that of Feltes [2003], which was described above, and Harris's [2011] retrospective cohort study.

The results of Feltes's study [2003] show that the size of the effect of palivizumab on the reduction of hospitalizations is much less pronounced during infants' second year of life. Furthermore, the absolute difference in the hospitalization rates between the two groups of Canadian infants is similar to that observed in the total population, which strengthens this study's external validity.

Harris's [2011] study was aimed at evaluating cost reduction at a tertiary care hospital and the cost-effectiveness of palivizumab after the introduction of an RSV immunoprophylaxis program in British Columbia in the fall of 2003. The subjects were children born at ≥36 weeks' gestation and who were <24 months of age at the start of the RSV season and had hemodynamically significant congenital heart disease. For the purposes of comparing the costs and RSV hospitalization-related outcomes, the study evaluated a cohort of infants who received palivizumab during the RSV seasons from October 2003 to May 2007 and a historical cohort of children who had not received palivizumab during the RSV seasons from October 1998 to May 2003, the number of subjects in which was established by estimation. The main results were as follows:

- The hospitalization rate in the children who received palivizumab was 1.7%, and that in the children who did not receive it was 2.9%.
- Of the 17 children hospitalized from 1998 to 2007, only 2 were 12 months of age or older.

The main weaknesses of Harris's study identified by INESSS were as follows:

- The publication does not indicate the method used to identify the study subjects or to confirm or rule out the presence of RSV by means of a test.
- To determine the number of patients who would have been eligible for palivizumab in the historical cohort, an estimate was made from the mean annual number of patients who had been eligible for it during the previous 3 years on the basis that the rate of heart disease remained stable over time.
- No statistical analysis of the results is mentioned.

On the other hand, the fact that the study was conducted at only one centre ensures clinical practice uniformity. Furthermore, there are similarities between the practice in British Columbia and that in Québec.

Despite these limitations, INESSS is of the opinion that the results concerning the number of children hospitalized according to their age are acceptable for demonstrating that hospitalizations do, in fact, occur less often during these children's second year of life.

Other publications

The analysis of a few North American observational studies also revealed that, in populations similar to those in the two studies mentioned above, children >12 months of age had a lower risk of being hospitalized for an RSV respiratory tract infection than younger children. The North American studies included, among others, those of Boyce [2000] and Wang [1997], the results of which are presented in the following table.

Results of the studies by Boyce [2000] and Wang [1997]

Author **Location** **Period**	**Age of children**	**Proportion of hospitalized children who did not receive palivizumab**
Boyce **Tennessee, U.S.** **July 1989 to June 1993**	<6 months	12.1%
	12-24 months	1.8%
Wang **Canada** **1993 to 1995 RSV seasons**	0-12 months	15.6%
	12-24 months	1.1%

In conclusion, the analysis of the results of all the above-mentioned studies reveals a consistently large difference between the RSV hospitalization rate during the second year of life of children with heart disease and that during their first year of life. Furthermore, the extent of the benefits of palivizumab is indeed smaller in older children, based on the results of the studies of Feltes and Harris. It will also be noted that all of these observations go back more than 10 years and that it is known that advances in the care of these children have been made since, so it would be surprising if this trend were to reverse itself.

D. Opinion of the Advisory Committee on the Use of Palivizumab

In the opinion of the pediatric cardiologists on the Advisory Committee on the Use of Palivizumab, the treatment of children with heart disease has improved since the publication of Feltes's study [2003], but the advances have been less extensive than the progress made for preterm infants. Consequently, the external validity of this trial is affected less than that of the IMpact-RSV study. Based on the analysis the results of Feltes's study stratified by the children's ages, the Committee had proposed, in 2015, lowering the palivizumab eligibility threshold and to thus reserve it for infants <12 months of age. Actually, it turns out that surgical correction is now almost always performed when the child is <12 months of age.

Furthermore, when analyzing the cases involving nonconforming requests approved during the 2014-2015 RSV season, INESSS had noticed that requests had been submitted to the evaluating physicians responsible for special cases, even though the justification provided may have been similar to the conditions in Criterion No. 4 in effect at the time. In 2015, the Committee's experts therefore felt that to ensure that palivizumab is used judiciously, requests concerning children with heart problems should be submitted only by pediatric cardiologists. Furthermore, to clearly define the diseases that can have significant hemodynamic consequences, the cardiologists were of the opinion that, in addition to congenital heart disease, the diagnoses of cardiomyopathy, myocarditis and moderate to severe pulmonary hypertension should be included. These measures could reduce the number of inappropriate nonconforming requests.

In 2016, the Committee's members did not change their opinion, and, to their knowledge, the application of the new 2015-2016 criterion has not caused any major problems.

E. INESSS's recommendation

In its preliminary report submitted to the MSSS in 2015, INESSS recommended the amendments proposed by the Advisory Committee, and the MSSS accepted them in their entirety and introduced them during the 2015-2016 RSV season. According to the Committee's experts, applying the new 2015-2016 criterion has not caused any major problems.

The results of INESSS's more in-depth analysis of the literature in 2016 support those of Feltes's study with regard to the lower hospitalization rate in older children. Furthermore, according to the data reported in Bellavance's study [2006], the inappropriate prescribing of palivizumab by cardiologists was far less frequent than that by pediatricians and general practitioners (combined). This observation therefore supports the relevance of allowing requests for palivizumab to be submitted only by pediatric cardiologists.

In conclusion, in INESSS's opinion, the eligibility criterion in effect during the 2015-2016 season should be maintained for the 2016-2017 RSV season, namely:

- *Infants <12 months of age at the start of the RSV season with hemodynamically significant congenital heart disease, cardiomyopathy or myocarditis or with moderate to severe pulmonary hypertension (the request must be submitted by a pediatric cardiologist to ensure the accuracy of the diagnosis).*

4.1.9 Immunocompromised children

A. Québec eligibility criteria

2014-2015 season	**Criterion No. 5** Children <24 months of age who have undergone a bone marrow or stem cell transplant during the 6 months preceding the RSV season or during the RSV season. Certain cases authorized upon a nonconforming request.
2015-2016 season	**Criterion No. 7** Children <24 months of age at the start of the RSV season who have undergone a bone marrow, stem cell or solid-organ (heart, liver or lung) transplant during the 6 months preceding the RSV season or during the RSV season.

B. Background

The analysis of the nonconforming cases authorized during the 2014-2015 RSV season revealed that requests had been approved for immunocompromised children for reasons other than those indicated in Criterion No. 5 (stated above), such as chemotherapy and leukemia. This finding led to an in-depth analysis of the relevance of modifying this criterion by adding other cases of immunodepression. It will be noted that the eligibility conditions in cases of immunodepression in the immunoprophylaxis programs in certain Canadian provinces differ from those in Québec's program (see Appendix III).

For the 2015-2016 season, the MSSS ratified the changes to eligibility Criterion No. 5 concerning transplant patients proposed by INESSS in August 2015 in its preliminary report, subject to the need to continue its analysis.

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

According to the AAP, palivizumab may be administered to children <24 months of age who are severely immunocompromised during the RSV season.

According to the CPS, palivizumab should not be administered routinely to children with immune deficits, with the exception of those <24 months of age who are on home oxygen, who are severely immunocompromised or who have required a prolonged hospitalization for severe pulmonary disease.

INESSS's systematic review of the scientific literature [2016]

No publication concerning this population was identified.

Other publications

Given the absence of studies on the use of palivizumab in immunocompromised children, INESSS chose to obtain data on the risk of hospitalization due to an RSV respiratory tract infection according to the cause of immunodepression. Of the few studies identified on this topic, INESSS selected the studies by

Asner [2013], El Saleeby [2008] and Hall [1986]. The methodological quality of the few published studies on HIV-infected children was really too low for these studies to be selected.

Asner's study [2013], a Canadian, single-centre observational study, was primarily aimed at documenting, over a 5-year period (2006-2011), the burden associated with RSV infections and to define their characteristics in a cohort of immunocompromised children <18 years of age. Included in the study were children hospitalized for an upper or lower respiratory tract infection, whether it was hospital- or community-acquired. The possible causes of immunodepression were autologous and allogenic bone marrow transplants, solid-organ transplants, chemotherapy, and long-term immunosuppression caused by a chronic illness or a congenital immunodeficiency. Children <5 years of age who were hospitalized for RSV infection and who were not eligible for palivizumab immunoprophylaxis were prospectively recruited, and data were collected retrospectively on the older children. The main results of this study were as follows:

- In all, 117 children were hospitalized for a screening test-confirmed RSV infection. The median age at the time of hospitalization was 2.7 years. The breakdown according to the cause of the immunodepression was as follows: bone marrow transplant (13.7%), solid-organ transplant (16.2%), solid tumors (16.2%), leukemia or lymphoma (28.2%), immunosuppression caused by a chronic illness (1.7%) and congenital immunodeficiency, including Down syndrome (13.7 %).
- Approximately 24% (n = 28) of the hospitalized children had a stay in an intensive care unit. Of this number, 35.7% had undergone a transplant, 14.3% had leukemia or a solid tumor, and the others had a congenital immunodeficiency, including Down syndrome.

Although the cohort included children up to 18 years of age, it is noted that half of the children were hospitalized at a young age, that is, before the age of 2.9 years. In addition, the results show a strong tendency for hospitalization in the children who had undergone a transplant or who had leukemia or lymphoma. A high proportion of them were admitted to an intensive care unit. It is difficult to comment on the children with various types of congenital immunodeficiency, since they were not defined. Children with Down syndrome were included in that group, and it is known that such children often have congenital heart disease or congenital morphological abnormalities that can constitute independent risk factors for severe infections. Unfortunately, no information is provided on the number of immunocompromised children who were not hospitalized. However, the results indicate that transplants and certain types of cancer were frequent causes of immunodepression in the hospitalized immunocompromised children in this study. Furthermore, these children seemed to have rather frequently severe RSV infections whose progression led to an ICU stay.

The objective of El Saleeby's single-centre, retrospective study [2008] was to provide and epidemiological overview of the screening test-confirmed RSV RTIs that occurred from 1997 to 2005 in immunocompromised children and to determine the predictive factors of the morbidity and mortality associated with such infections. Eligible children had to be <21 years of age and have one of the following immunodepression factors: neoplasia, hematological disorder, stem cell transplant or immunodeficiency syndrome. Infections were categorized according to whether they affected the upper or lower respiratory tract. Furthermore, the cohorts of children were stratified according to whether or not they were <24 months of age. Lastly, the patients were divided into three groups according to their degree of immunodepression: those with a solid tumour, those with acute lymphoblastic leukemia (ALL), and those with acute myeloid leukemia (treated with highly cytotoxic

drugs) or severe combined immunodeficiency syndrome (SCIS) or who were being prepared for a stem cell transplant and up to 24 months after the transplant. The main results of this study were as follows:

- In all, 58 children met the inclusion criteria. The only risk factors for RSV lower RTI, considered to be independent, based on a multivariate analysis, were young age (<24 months) and severe lymphopenia (lymphocyte counts <100 cells/μL, with odds ratios of 9.84 (95% CI: 1.95 to 49.8) and 7.17 (95% CI: 1.17 to 44.03), respectively).
- The multivariate analysis showed no correlation between neutropenia and the occurrence of lower RTIs. The same was true for the cause of the immunodepression.
- All the deaths occurred in the third group.
- A lower RTI occurred in 42% of the children in the third group, in 36.4% of the children with a solid tumour, and only 8.7% of the children with ALL.
- Of all the children included, 36% were hospitalized and 22% required oxygen therapy.

The prospective study by Hall [1986] was aimed at it assessing the severity of RSV infections in immunocompromised children compared to healthy children according to different causes of immunodepression. The children were <5 years of age, had to have been hospitalized during the winter in 1974 to 1984 for confirmed hospital- or community-required RSV infection. They were divided into three groups according to the cause of their immunodepression: 1) a congenital immunodeficiency, such as SCIS; 2) corticosteroid therapy of at least 30 days' duration; and 3) chemotherapy for cancer. A control group of healthy children was formed. The main results of this study were as follows:

- Of the 1718 children hospitalized for an acute respiratory tract infection, 47 were immunocompromised. Of this number, 20 were on chemotherapy, 22 were on corticosteroid therapy, and 5 had a congenital immunodeficiency disorder. Of all the children in the cohort, 608 were infected with RSV. They included all those on chemotherapy or with an immunodeficiency disorder and 12 of those receiving steroids.
- Close to 50% of the children on chemotherapy were ≥24 months of age at the time of their hospitalization. This percentage was 17% and 25% for those treated with corticosteroid therapy and those with an immunodeficiency disorder, respectively.
- No statistically significant difference was observed between the immunocompromised children <24 months of age and the healthy children.

Although this study dates back a few decades and no difference was observed between the immunocompromised children and the healthy children in terms of the incidence of hospitalizations that occurred before the age of 24 months, some of the results reported may be useful for reevaluating Criterion No. 5. It will be noted that the absence of a difference could have resulted from the study's lack of statistical power. Nevertheless, it seems that the age, at the time of hospitalization, of the children on chemotherapy was higher than that of the other immunocompromised children. Knowing that palivizumab is recommended before the age of 24 months in all the guidelines, regardless of the underlying health problem, the children on chemotherapy would not systematically be eligible for immunoprophylaxis. As for children with SCIS, they are now hospitalized in a protected environment until the transplant. Therefore, given their isolation, palivizumab would not be clinically indicated. There remains the group of children who were on corticosteroid therapy, in which only 55% of the children were hospitalized as opposed to 100% of those in the other groups. This suggests that the

immunosuppression associated with corticosteroid therapy is a risk factor of lesser importance for severe RSV infection than the other causes of immunodepression.

In conclusion, the results of the studies examined show that certain causes of immunodepression seem to predispose to severe infections. Corticosteroid therapy does not seem to be one of those that increase the risk of RSV hospitalization the most. The children who were on chemotherapy tended to be older than 24 months, the maximum age for palivizumab eligibility. This is why INESSS feels that adding these two populations to the criterion for immunocompromised children would not be justified on the basis of the scientific data. Furthermore, from a clinical standpoint, INESSS recommends palivizumab immunoprophylaxis in the children it considers to be at greatest risk for a severe infection. It therefore considers that children who have undergone a bone marrow or solid-organ transplant are more likely to be severely immunosuppressed because of the highly immunosuppressive therapy they receive.

D. Opinion of the Advisory Committee on the Use of palivizumab

The Committee's clinicians proposed that palivizumab prophylaxis for the children concerned by Criterion No. 5 (above) be maintained and that children <24 months of age who have undergone a heart, liver or lung transplant be added, although such cases are rather rare. The intensive immunosuppression that follows constitutes a significant risk factor for the exacerbation of infections. However, these clinicians feel that there would be no need to add to this criterion other causes of immunodepression identified in the above-mentioned studies, because of the weakness of the evidence. Furthermore, the incidence of the cases encountered in their practice is very low. Consequently, a clinical assessment should be made on a case-by-case basis.

The relevance of offering palivizumab to children who have received a transplant more than 6 months before the RSV season was raised, since the immunosuppression that follows lasts for more than 6 months. Lastly, the statu quo was chosen because the risk of severe infection associated with immunosuppression is greater during the first few months following a transplant.

In conclusion, the Committee's experts propose the following palivizumab immunoprophylaxis criterion for immunocompromised children:

- *Children <24 months of age at the start of the RSV season who have undergone a bone marrow, stem cell or solid-organ (heart, liver or lung) transplant during the 6 months preceding the RSV season or during the RSV season.*

E. INESSS's recommendation

Given that it is very unlikely that a randomized, controlled trial of good methodological quality will be conducted to assess the benefits of palivizumab immunoprophylaxis in immunocompromised children, INESSS is of the opinion that Criterion No. 7, which was in effect during the 2015-2016 RSV season, be maintained for the next season.

4.1.10 Infants in remote communities

A. Québec eligibility criteria

2014-2015 season	Certain cases authorized upon a nonconforming request.
2015-2016 season	Certain cases authorized upon a nonconforming request.

B. Background

In June 2006 and 2009, the Conseil du médicament recommended to the Minister of Health and Social Services that an in-depth analysis be performed of the relevance of instituting a palivizumab immunoprophylaxis program for young children in Québec's Far North, given the particular characteristics of this region. There is currently no specific immunoprophylaxis program in Nunavik. Its infants are subject to the eligibility conditions in the program for the entire Québec population. It will be noted that the palivizumab immunoprophylaxis program in certain Canadian provinces contains specific eligibility criteria for infants living in isolated areas and that Nunavut has its own program (see Appendix III).

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

The AAP does not officially recommend the use of palivizumab to protect the Alaska Native population or Amerindian populations on U.S. territory. However, it does call attention to the fact that the burden associated with severe RSV infections and the costs associated with the air transportation required to hospitalize children with such infections who live in remote communities could justify broader use in these populations.

According to the CPS, palivizumab should be offered to infants born at <36 weeks' gestation and <6 months of age at the start of the RSV season in remote communities where air transportation would be required for hospitalization. The CPS does not know whether this recommendation should apply only to Inuit infants, to all Aboriginal infants or to all infants in remote communities. The incidence of RSV hospitalizations in a remote community during the previous years should be taken into account when making this decision. Furthermore, the CPS adds that consideration can be given to administering palivizumab to Inuit term infants until they reach the age of 6 months, if they live in communities where persistently high rates of RSV hospitalization have been documented. However, in the CPS's opinion, the priority should be to offer palivizumab to preterm infants and to infants with hemodynamically significant heart disease or with bronchopulmonary dysplasia.

INESSS's systematic review of the scientific literature [2016]

Only two publications were selected for the systematic review, those of Banerji [2014] and Singleton [2003].

Banerji's observational study [2014] sought to evaluate the efficacy of palivizumab in Nunavut infants in reducing hospitalizations for RSV lower respiratory tract infections during two RSV seasons (2009-

2010). In addition to being <6 months of age at the start of the RSV season, eligible infants had to have a gestational age <36 weeks and cardiac or pulmonary disease. Only infants who contracted a screening test-confirmed RSV infection were selected. The hospitalization rate observed in the infants who did not receive palivizumab or who were not adequately prophylaxed was 50% (5/10), while that for the infants who were adequately prophylaxed was 2.2% (2/91), for an OR of 22.3 (95% CI: 3.8 to 130; p = 0.0005).

The methodological quality of this study is considered poor. The results show that the hospitalization rate for the Nunavut infants who received palivizumab was not higher in number than that observed in observational studies involving similar cohorts of Canadian infants. One of this study's weaknesses is that the actual number of infants eligible for palivizumab immunoprophylaxis is unclear. To perform a sensitivity analysis, the author estimated that the maximum number of eligible infants could have been 130. Therefore, 28 infants would be missing, and the failure rate for palivizumab in the worst-case scenario would have increased to 17%. On the other hand, the imputation of these missing data to the group of infants who did not receive immunoprophylaxis could have resulted in an overestimation of the hospitalization rate (50%) associated with it. It will be noted that the screening tests in 2 of the 5 non-prophylaxed infants who were hospitalized revealed the co-presence of types of respiratory viruses other than RSV. It is therefore possible that these infants would have been hospitalized just the same if they had received palivizumab. Several viruses were also detected in 1 of the 2 hospitalized infants who received palivizumab. Furthermore, the study does not provide any information on the presence of environmental factors known to increase the risk of RSV hospitalization, with the result that it cannot be determined if there was a bias between the two groups of infants in this regard. It will be noted that, of the 7 hospitalized infants, 4 would have been eligible for palivizumab during the last RSV season in Québec. In conclusion, the results should be interpreted with caution because of the multiple sources of uncertainty.

The objective of Singleton's retrospective observational study [2003] was to assess the impact of palivizumab use on the number of hospitalizations due to an RSV infection (confirmed by a screening test) that occurred before the age of 12 months during the RSV season (October to May) in Alaska Native infants born between June 1 and May 31 who were considered to be at high risk for RSV infection. Two cohorts were compared for this purpose. One consisted of infants who were eligible to receive palivizumab according to the conditions in effect during the 1998-2001 RSV seasons. They were preterm infants 1) born at ≤32 weeks' GA; 2) born at 33 to 35 weeks' GA and diagnosed at birth with respiratory distress syndrome, bronchopulmonary dysplasia, interstitial emphysema, twin birth or congenital heart disease or a congenital abnormality; 3) born at 36 weeks' gestation and have pulmonary disease (neonatal pneumonia, pneumothorax or respiratory distress syndrome). The other cohort consisted of infants who met these conditions but who did not receive palivizumab during the three RSV seasons (1993-1996) before the program was introduced. The main results of the study were as follows (it will be noted that only the first hospitalization was considered when there were more than one):

- In the rural region of the Yukon Kuskokwim (YK) Delta, the hospitalization rate among the high-risk preterm infants born at <36 weeks' gestation was 43.9% before the palivizumab immunoprophylaxis program was introduced compared to 15% after it was introduced, for an absolute difference of 29.9%, a relative risk (RR) of 0.34 (95% CI: 0.17 to 0.68) and an NNT of 3.4.

- Introducing the immunoprophylaxis program had no influence on the hospitalization rate among the non-preterm infants (born at ≥36 weeks' gestation) in the YK Delta region. This rate remained stable at about 15%.
- The hospitalization rate among the 335 infants in all of Alaska who were eligible for palivizumab during the 1998-2001 RSV seasons was 12.5% (42/335). The hospitalization rate among the preterm infants with or without pulmonary disease was 13% (7/54) and 7.6% (17/225), respectively, and that among the term infants with pulmonary disease was 48.3 % (14/29).

The methodological quality of this study was considered poor. INESSS identified several weaknesses, including the following:

- An RSV screening test was not systematically performed, but at least the proportion of hospitalizations with no test was similar in each of the cohorts of YK Delta infants, that proportion being approximately 18%. Furthermore, this proportion was not reported for the entire cohort of infants in the state of Alaska.
- The detailed results concerning hospitalizations in the cohort of infants for all of Alaska during the 1993-1996 RSV seasons were not published, with the result that no comparisons can be made with the cohort of infants who received palivizumab during the 1998-2001 seasons. The evaluation of the effect of palivizumab would have concerned a greater sample than that from the YK Delta region. This would also have made it possible to determine the difference in the results between a rural region, whose population is 85% Yup'ik, and a Nordic country.
- As in Banerji's study, no information is provided about the presence of environmental factors known to increase the risk of RSV hospitalization, with the result that it cannot be determined if there was a bias between the groups.

The results indicate that the hospitalization rates were very high in the YK Delta region compared to those reported in studies conducted in southern urban areas with non-Native populations. The hospitalization rates were also higher, but to a lesser degree, among Alaskan infants who received palivizumab. Despite the above-mentioned limitations, INESSS is of the opinion that the efficacy of palivizumab in reducing RSV hospitalizations has been demonstrated in high-risk preterm infants with a GA <36 weeks in the rural Native population. However, no difference was observed in the non-preterm infants in this region after the introduction of the palivizumab immunoprophylaxis program. In the cohort of Alaskan infants who received palivizumab, close to half of the term infants with pulmonary disease were hospitalized. This was the highest hospitalization rate in this cohort. Given the absence of a comparison group, it is difficult to conclude that palivizumab is not efficacious in these infants.

Other publications

Banerji's prospective, multi-hospital surveillance study [2013] compared the rate and duration of hospitalizations due to a lower respiratory tract infection in infants <12 months of age in certain Arctic regions of Canada, namely, the Northwest Territories, Nunavut and Nunavik, from June 1, 2009 to June 30, 2010. The hospitalization rate per 1000 live births in Nunavik was the highest, 445, compared to 236 in Nunavut and 38 in the Northwest Territories. It will be noted that the proportion of Inuit is 80 to 90% in the first two regions but only 10% in the third. Although this study does not report any specific results concerning RSV hospitalizations, it is known that this virus is the most common one in these

infants. It can therefore be concluded fairly safely that Inuit infants in Nunavik are indeed a population at much greater risk than other Canadian infants.

D. Context of remote Aboriginal communities

In April 2016, INESSS requested the collaboration of a pediatrician because of her expertise in the Northern and Native Health Program in order to obtain an overview of the situation with palivizumab immunoprophylaxis in the pediatric population in Québec's Far North and of the specific context of this environment.

Nunavik has 14 Inuit communities and the Cree village of Whapmagoostui, part of which is in Nunavik, the other part being in the Terres-Cries-de-la-Baie-James region. Each village is served by a CLSC (24-hour emergency service) or primary care nurse clinicians and by two regional hospitals (Ungava (Kuujjuaq) and Hudson Bay (Puvirnituq)), where family physicians, among others, practice. Therefore, not every community has a physician.

- As for the communities in the Terres-Cries-de-la-Baie-James region, secondary care services are provided by the Hôpital de Val-d'Or and the Hôpital de Chibougamau, and the designated tertiary referral centre is the Montreal Children's Hospital. If its intensive care unit is over-capacity, infants are referred to the CHU Sainte-Justine or to a tertiary care centre in Quebec City. Infants are always transferred to these hospitals by airplane.
- As regards the communities in Nunavik, infants are usually treated at a regional hospital first. Those in isolated communities (with no road access) are transported to this hospital by airplane, while those near regional hospitals are taken there by road transport. Next, if necessary, the infant is transferred by airplane to the Montreal Children's Hospital.
- The CLSCs automatically transfer infants to a regional hospital (or directly to the tertiary referral centre in certain cases) if they require more than 6 hours of care. The decision to transfer a child to a regional hospital or a tertiary care centre is made by physicians. Often, they do this quickly, for different reasons, such as any delay increasing the risk of complications or the airplanes running on a fixed schedule. Unless there are weather or other constraints, two regular daily flights are systematically scheduled to link the populations in the communities that do not have a road system. Among other things, these flights are used to transfer children to the Hôpital de Val-d'Or or the Hôpital de Chibougamau or to the tertiary referral centre. If the infant requires rapid care and the situation arises between the regular flights, a chartered airplane is used, whose services are far more expensive. A nurse may have to accompany the mother and infant. If an infant requires intensive care, an air ambulance (EVAQ-Challenger) is used to transfer him/her to a tertiary care centre. As for the accompanying parent, he/she has to take another airplane. The meal, accommodation and transportation costs are assumed by the federal government. A change of escort is allowed every other week and therefore results in additional expenses, to say nothing of the fact that an escort may have to be paid. Social costs must be considered. For example, it is the mothers who generally accompany the infant, and they are usually the ones who have a job. They also have to have other people look after their other children, of which there is often a large number. Furthermore, if the mother of a sick infant is a teacher or is responsible for a daycare centre, these services will not be offered while she is at her infant's bedside.

Health need

In the opinion of the expert consulted, there are no problems accessing palivizumab for infants in Québec's Far North with a GA <36 weeks who are considered to be at risk for hospitalization. Either their health meets the eligibility criteria exactly or a nonconforming request is submitted on Form B. Nonconforming requests are very rarely turned down. It was, in fact, through this process that preterm infants of 33 to 35 weeks' GA were authorized palivizumab during the 2015-2016 RSV season. According to the pediatrician's recollection, none of the infants who received palivizumab was hospitalized at the Montreal Children's Hospital and no deaths have been reported during the past 10 years.

Currently, the greatest unmet health need is immunoprophylaxis in young term infants with no medical risk factors for severe infection that could lead to hospitalization. This opinion is based mainly on clinical data—from medical records at the above-mentioned referral centre—concerning RSV hospitalizations during the period from January 1, 2006 to April 28, 2016. It will be noted that the following statistics may be underestimations for different reasons (e.g., a single tertiary care centre).

- Over a 10-year period, 82 infants were hospitalized: 26 Cree (15 of whom were hospitalized in a pediatric intensive care unit) and 56 Inuit (36 of whom required intensive care). Although there are more Cree than Inuit, proportionately, the latter are hospitalized much more often.
- Out of an annual total of approximately 350 live births, about 1.5% of Inuit infants were transferred to the Montreal Children's Hospital, and about 1% of Inuit infants were admitted to the intensive care unit.
- Of the hospitalized Inuit infants, 66% were <3 months of age (27% during the first month and 22% during the second month).
- The mean length of hospital stay is approximately 12 days.
- Infants are hospitalized mostly in January, February, March and April (peak in February and March).

Based on the analysis of the contextual and experiential data presented above, the following were proposed:

- Take into account the fact that the RSV season does not coincide with that in more southern regions when determining the palivizumab immunoprophylaxis period: from December 1 to April 30 instead of from November 1 to March 31.
- Administer palivizumab very soon after birth or very shortly before the infant's discharge from hospital, taking into account the period that constitutes the RSV season.
- Administer at least three doses, always taking into account the period constituting the RSV season.
- Cover term infants <3 months of age at the start of the RSV season for one season.

Organization of care pertaining to palivizumab immunoprophylaxis

According to the expert consulted, the organization of care in Québec's Far North is not an impediment to the success of an immunoprophylaxis program suited to this region. First, there is intensive screening of infants at risk for RSV bronchiolitis. Since health care is provided at a small number of facilities (centralization of medical activities), the task is easier, even more so than in southern regions. Furthermore, the Aboriginals are very cooperative, as evidenced by their very high vaccination participation rate of more than 90%. These peoples have been badly decimated several times by different diseases, and they have a heightened awareness of prevention. Lastly, the health professionals involved regularly take ongoing training on immunoprophylaxis-related topics. Furthermore, if they were asked to keep a registry for following the pediatric population targeted by the immunoprophylaxis program, as is done elsewhere in Canada, and to routinely perform RSV screening tests, the expert feels that these tasks could be performed without requiring a great deal of work.

E. Opinion of the Advisory Committee on the Use of Palivizumab.

Particular attributes of infants in Québec's Far North

The Committee's experts emphasize the fact that the living conditions of Inuit infants contributes to increasing their risk of hospitalization during an RSV infection, among other things, because of the large number of people living in the same dwelling and because of smoking. Furthermore, their hospitalization rate, one of the highest in the world, is, perhaps, also due to a genetic immunodeficiency. Their risk of hospitalization is reportedly 4 to 5 times higher than that of infants in the southern regions of Québec. In addition, the criteria to be used when deciding to hospitalize an infant are more flexible in Nunavik. Nonetheless, infants transferred to the tertiary care centres are very sick when they arrive there, since the amount of time between the hospitalization decision and the transfer is often too long, given the constraints of the air transportation schedule. Therefore, they often require a stay in an intensive care unit, with the result that a scheduled operation for another infant is delayed because of a lack of care spaces in that unit.

It has been clearly established that Inuit infants are at very high risk for hospitalization due to an RSV respiratory tract infection, often for a prolonged period and with complications. It is reportedly the pediatric population at greatest risk of all. Furthermore, experts are of the opinion that Inuit infants differ from Cree infants because the risk of hospitalization in the former is proportionately higher and because these infants experience more complications. In this connection, a 10-year follow-up study in the Nunavik and Terres-Cries-de-la-Baie-James regions ended in 2014. The results concerning RSV hospitalization rates in the Inuit and Cree, the hospitalizations that required a transfer to a tertiary care centre, the inherent costs and other parameters will not, however, be available until the fall.

Conditions of eligibility for Aboriginal infants in remote regions

In 2015, the Committee's members proposed that the criterion stated below be added to the palivizumab immunoprophylaxis program, given the specific context of Québec's Far North region and its remoteness, the high-risk factors for the hospitalization of the Aboriginals who live there, and their proposal to revoke Criterion No. 2 concerning preterm infants of 33 to 35 weeks' GA. It will be noted

that the infants in question are already receiving palivizumab because in actual fact, nonconforming requests concerning them are almost always approved. By formalizing this criterion, such requests would no longer be necessary.

- *Québec Far North infants born at ≤36 weeks' gestational age who are <6 months of age at the start of the RSV season or born during the RSV season.*

In 2016, focusing on infants at greatest risk for being hospitalized, and upon considering the expert's experience in the Quebec's Far North context, the clinicians unanimously proposed that palivizumab prophylaxis also be offered to term infants <3 months of age at the start of the RSV season or born during the RSV season.

Furthermore, in view of the financial burden associated with hospitalizations from the perspective of the cost-effectiveness of immunoprophylaxis, all the Committee's members consider that palivizumab prophylaxis should be reserved for infants, only if health care in severe cases requires travel by air transportation. Consequently, the proposed criteria would be adjusted as follows:

- *Infants born at ≤36 weeks' gestational age who are <6 months of age at the start of the RSV season and who reside in a remote region where access to health care, given the severity of their condition, requires air transportation.*
- *Infants born at term who are <3 months of age at the start of the RSV season or born during the RSV season and who reside in a remote region where access to health care, given the severity of their condition, requires air transportation.*

Details of administration of palivizumab

The details of administration specific to the above-mentioned infants are spelled out in Section 4.2.

F. INESSS's recommendation

The level of evidence of the scientific data is low. However, despite the limitations of the above-mentioned studies, INESSS is of the opinion that the efficacy of palivizumab prophylaxis in reducing RSV hospitalizations has been demonstrated in high-risk preterm infants of <36 weeks' GA in the rural Inuit pediatric population in remote northern regions. Given the ongoing study in Québec's Far North region, whose results will be available shortly, INESSS feels that it is more prudent for now to recommend the use of palivizumab, for the next RSV season, in Nunavik infants only, according to the following criterion:

- *Nunavik infants born at ≤36 weeks' gestational age who are <6 months of age at the start of the RSV season or born during the RSV season*

However, the results of Singleton's study did not show a difference in the RSV hospitalization rates before and after the introduction of the palivizumab immunoprophylaxis program in non-preterm infants in the rural region of Alaska's YK Delta. Nonetheless, based on the experiential data provided to it on term infants in Québec's Far North, INESSS, like the experts consulted, feels that it is reasonable to offer immunoprophylaxis to term infants considered to be at greatest risk for hospitalization. However,

INESSS is of the opinion that, to start, this recommendation is intended only for Nunavik infants according to the following criterion:

- *Nunavik term infants who are <3 months of age at the start of the RSV season or born during the RSV season*

4.1.11 Children with Down syndrome

A. Québec eligibility criteria

2014-2015 season	Cases authorized upon a nonconforming request
2015-2016 season	No known cases authorized upon a nonconforming request

B. Background

The analysis of nonconforming requests approved during the 2014-2015 RSV season revealed that some involved children with Down syndrome. Several of these children had several comorbidity factors. This finding warranted an in-depth analysis of the relevance of including or not including a specific eligibility criterion for these children.

C. Scientific publications selected

AAP [2014] and CPS [Robinson* et al.*, 2015] guidelines

The AAP's recommendation is as follows:

- Palivizumab should be administered to children with Down syndrome only if they have heart disease or chronic lung disease or impaired clearance of airway secretions or if they were born at <29 weeks' GA.

The CPS's recommendation is as follows:

- Palivizumab should not be administered routinely to children with Down syndrome. It may be reasonable to administer it to those <24 months of age at the start of the RSV season and who are on home oxygen or who have had a prolonged hospitalization for severe pulmonary disease or if they are severely immunocompromised.

INESSS's systematic review of the scientific literature [2016]

A single study concerning children with Down syndrome was identified, that of Yi [2014].

This was an observational study aimed at comparing the effect of palivizumab on the occurrence of hospitalizations due to a test-confirmed RSV RTI in a cohort of Down syndrome children <24 months of age who prospectively received palivizumab versus a similar control cohort of children who did not received it. The treated cohort (n = 532) was a subset of the children in the Canadian registry CARESS (2005-2012) [Mitchell *et al*., 2011]. The control cohort (n = 233) consisted of Dutch children from Bloemers's prospective study [2007], which was conducted from 2003 to 2005. In addition to Down

syndrome, the children in both cohorts may have had health problems considered risk factors for severe RSV infection, such as hemodynamically significant heart disease, chronic pulmonary disease, multisystem anomalies or prematurity (GA of ≤35 weeks). The main results of the study were as follows:

- The hospitalization rate in the children who did not receive palivizumab was higher than in the nonrecipients: 9.9% (23/233) versus 1.5% (8/532), for an incidence rate ratio of 3.63 (95% CI: 1.52 to 8.67) adjusted according to certain variables.
- The adjusted incidence rate ratio in the subgroups of children with common risk factors (hemodynamically significant heart disease, chronic pulmonary disease, prematurity) was similar to that in the total cohorts.
- No difference was observed between the RSV hospitalization rates in the two subgroups of children with none of the above-mentioned risk factors (adjusted incidence rate ratio of 6.57 [95% CI: 0.70 to 62.16]).

The methodological quality of this study is considered poor. It does have certain positive aspects, such as prospective data collection in both cohorts and a statistical analysis that took certain confounding variables into account, but it has many limitations, such as the following:

- The two cohorts did not come from the same country, and the follow-up periods were different. There may have been differences in the hospitalization criteria as well.
- The higher prevalence of some of the risk factors in the palivizumab cohort may have contributed to underestimating the drug's effect.
- The statistical power may have been insufficient for detecting a difference between the subgroups of Down syndrome children who did not have any of the determined risk factors.
- No information is provided on the criteria used to form the control cohort from the population in Bloemers's study [2007].

The manifestations of Down syndrome, such as hemodynamically significant congenital heart disease, gastroesophageal reflux and congenital malformations of the upper airways, are diverse. The frequency and severity of these problems vary. INESSS was therefore interested in knowing if, in the absence of the known risk factors, Down syndrome is, in itself, an independent risk factor and if palivizumab could confer benefit in this context. Palivizumab was beneficial in the children in the total cohort who received it. This effect was predictable because a high proportion of this population had health problems known to be risk factors for severe infection. The similarity in the hospitalization incidence ratios obtained in the total cohorts and the subgroups of high-risk children was an indication of this. However, the incidence rate ratio in the subgroups of children with no comorbidity factors was very uncertain. The large confidence interval obtained very likely indicates a lack of power.

In conclusion, the results of this study are not very useful for clinically or scientifically justifying the use of palivizumab prophylaxis in young children with Down syndrome who have no comorbidity factors known to increase the risk of severe infection.

D. Opinion of the Advisory Committee on the Use of palivizumab

According to the experts consulted, approximately 60% of Down syndrome children have a risk factor that makes them eligible for palivizumab under the criteria that were in effect during the last RSV season, such as heart disease, hypotonia or a congenital anomaly that impairs the clearance of secretions. As for the remaining 40%, the literature examined does not justify the relevance of using palivizumab in these children. Furthermore, unlike certain hereditary metabolic diseases, Down syndrome is not a genetic disease that can be decompensated during a severe infection. In light of the foregoing, and based on the principle that palivizumab should be reserved for children at high risk for hospitalization, the Committee's members are still of the opinion that it would be inappropriate to add a specific eligibility criterion for Down syndrome children with no comorbidity factor known to increase the risk of hospitalization during an RSV infection.

E. INESSS's recommendation

After analyzing the literature, INESSS is not in a position to recognize the therapeutic value of palivizumab prophylaxis in young Down syndrome children with no risk factors for severe infection. This is why INESSS agrees with the experts' opinion and recommends not adding a criterion for this population.

4.1.12 Children with a metabolic disease

A. Québec eligibility criteria

2014-2015 season	Certain cases were authorized upon a nonconforming request when the disease was considered be at high risk for decompensation.
2015-2016 season	No requests known to have been submitted.

B. Background

In its report to the Minister of Health and Social Services in 2006, the Conseil du médicament was of the opinion that there was no justification for developing a palivizumab eligibility criterion for children with a metabolic disease, given the absence of evidence supporting such use. A list of metabolic diseases considered to be at high risk for decompensation during a severe infection had been prepared by geneticists to aid in the evaluation of nonconforming requests.

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

Neither of these organizations has issued recommendations concerning children with a metabolic disease.

INESSS's systematic review of the scientific literature [2016]

No publications concerning this population were identified.

Other publications

According to the results of Kristensen's study [2012], which was presented and analyzed above in Section 4.1.6 C, the ratio of the hospitalization incidence rate in children with certain inborn errors of metabolism, such as of amino acids and fatty acids (E70-E73.0, according to the ICD-10 classification), to that in children with no inborn errors of metabolism indicated a statistically higher risk of RSV hospitalization in the presence of one of these disorders.

D. Opinion of the Advisory Committee on the Use of palivizumab

Decompensation of certain metabolic disorders may be caused by any severe viral or bacterial infection, not specifically by RSV infection. In children with certain metabolic diseases, the administration of palivizumab is not primarily intended to reduce the number of hospitalizations, but rather to prevent an infection whose symptoms would be so severe as to cause decompensation of the disease. No scientific data supports such use. However, the experts are of the opinion that the process for authorizing requests on a case-by-case basis in this population be maintained, subject to a review of the list of metabolic diseases at greatest risk for significant decompensation.

E. INESSS's recommendation

INESSS recommends that an eligibility criterion for children with certain metabolic diseases not be added and that requests concerning such children continue to be authorized on a case-by-case basis, subject to an update of the list of these diseases by geneticists, the list to take into account the burden caused by the occurrence of decompensation and contemporary advances in the treatment of these diseases.

4.1.13 Infants of a multiple birth

A. Québec eligibility criteria

2014-2015 season	Nonconforming requests were submitted in cases involving a healthy twin of a palivizumab-eligible infant.
2015-2016 season	No known authorized cases

B. Background

A considerable number of nonconforming requests for the healthy twin of a palivizumab-eligible infant were approved. This finding led to an in-depth analysis of the relevance of adding a palivizumab eligibility criterion for these infants. It will be noted that they are included in the immunoprophylaxis program in certain provinces (see Appendix III).

C. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

These organizations have not published any usage recommendations concerning these infants.

INESSS's systematic review of the scientific literature [2016]

No publications concerning this population were identified.

Other publications

No publications justifying the use of palivizumab in a healthy twin of a palivizumab-eligible infant were identified.

D. Opinion of the Advisory Committee on the Use of palivizumab

Since palivizumab does not prevent RSV transmission, the experts consulted feel that there is no justification for using it in this context. Hygiene measures are to be encouraged instead. Therefore, they proposed that palivizumab no longer be authorized for the healthy twin of a palivizumab-eligible infant.

E. INESSS's recommendation

INESSS has ratified the experts' suggestion.

4.2 OPTIMIZING THE DETAILS OF ADMINISTRATION OF PALIVIZUMAB

4.2.1 Administration of palivizumab to children ≥24 months of age

A. Background

The analysis of the nonconforming requests revealed that several of them concerned children who were ≥24 months of age during the last RSV season, but these requests were not authorized.

B. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

None of these guidelines recommends the administration of palivizumab to children aged ≥24 months at the start of the RSV season.

C. Opinion of the Advisory Committee on the Use of palivizumab

The experts consulted feel that it is inappropriate to prescribe palivizumab prophylaxis at the age of ≥24 months, since there is no evidence supporting such use. Furthermore, at this age, children are

heavier, the diameter of their airways is larger and they may have produced antibodies against the RSV. They are therefore better able to tolerate the symptoms of RSV infection.

D. INESSS's recommendation

INESSS shares the opinion of the experts consulted. To prevent the submission of unjustified nonconforming requests and to thus reduce the number of evaluations by designated evaluating physicians, INESSS recommends adding an exclusion clause concerning children ≥24 months of age in the Héma-Québec circular containing the palivizumab eligibility criteria.

4.2.2 Continuation of the administration of palivizumab after the occurrence of RSV infection

A. Scientific publications selected

AAP [2014] and CPS [Robinson* et al.*, 2015] guidelines

Contrary to what is indicated in the Synagis® product monograph, the AAP and CPS do not recommend, in infants hospitalized for RSV infection despite having been prophylaxed, to continue administering palivizumab during the RSV season because recurrences of RSV infection during a given season are uncommon (<0.5%). According to the CPS, the NNT would undoubtedly be very high if prophylaxis were to be continued in this context.

B. Opinion of the Advisory Committee on the Use of palivizumab

According to the experts consulted, there is cross-immunity between RSV-A and -B genotypes. Although two episodes of RSV infection can occur during a given season, the infant has usually gained weight by the second episode and is therefore better able to tolerate the symptoms, which are generally less severe than during the first episode. Before stopping prophylaxis in an infant who has contracted RSV infection, he/she must have required hospitalization for his/her condition and the presence of the RSV must have been confirmed by a screening test.

C. INESSS's recommendation

INESSS agrees with the Advisory Committee. Therefore, the guidance on discontinuing the administration of palivizumab in the circumstances described above should continue to appear in the Héma-Québec circular. However, INESSS feels that this guidance should be modified slightly to reflect the opinion of the Advisory Committee, the AAP and the CPS, all of which recommend discontinuing the prophylaxis, not only if the presence of RSV has been confirmed, but also if the infant had to be hospitalized for RSV infection. Consequently, the guidance should read as follows:

- *Palivizumab prophylaxis should be discontinued after an infant has been hospitalized for a screening test-confirmed RSV respiratory tract infection.*

4.2.3 Administration of palivizumab during hospitalization

Because of the absence of specific guidance in the Héma-Québec circular containing the palivizumab eligibility criteria, there are differences between the practices at the different neonatology centres in terms of when the first dose of palivizumab is administered to eligible infants who are hospitalized there. This explains why palivizumab may have been administered during a hospital stay to prevent nosocomial RSV infections.

A. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

As regards the first situation mentioned above, the CPS recommends initiating palivizumab prophylaxis right before discharge from hospital. The AAP is of the same opinion, although it adds the option of initiating it very shortly after discharge.

As for preventing nosocomial infections, the CPS does not recommend palivizumab for this use, since it would be an expensive strategy. The AAP has not addressed this topic.

B. Opinion of the Advisory Committee on the Use of palivizumab

The experts consulted agreed with the CPS's recommendations. They indicated that palivizumab should be administered within 48 to 72 hours before the eligible infant is discharged from hospital and that the date of administration of the second dose should be set immediately at that point. It will be noted that the recommended interval is the same as that mentioned in British Columbia's palivizumab immunoprophylaxis program.

C. INESSS's recommendation

INESSS is of the opinion that the Héma-Québec circular should mention the following in order to optimize the use of palivizumab:

- *Palivizumab should be administered within 48 to 72 hours before a palivizumab-eligible infant is discharged from hospital.*
- *Administering palivizumab to prevent nosocomial RSV infections is not indicated.*

4.2.4 Details of administration of palivizumab: number of doses and dosing intervals, determining the RSV season, administration schedule, etc.

A. Context

Due to a lack of guidance, we observed disparities between the different regions or hospitals, notably, in terms of the details of administration of palivizumab. For example, one Advisory Committee member reported that 50 to 60% of infants receive 6 doses per season instead of the 5 recommended in the product monograph provided by the manufacturer. Furthermore, it emerged from discussions with the experts consulted in 2015 that there was a problem accessing palivizumab prophylaxis because of a

lack of cooperation on the part of certain health-care facilities that were not making it a priority. As well, some of those that offer palivizumab reportedly impose a quota.

B. Scientific publications selected

AAP [2014] and CPS [Robinson et al.*, 2015] guidelines*

The CPS recommends a maximum of 3 to 5 doses per season (15 mg/kg/dose), 4 doses probably being sufficient to protect all at-risk groups when palivizumab is administered only in the presence of RSV activity in the community, especially when the second, third and fourth doses are administered at 38-day intervals. There is no evidence supporting the administration of more than 5 doses in a given RSV season.

The AAP recommends a maximum of 5 doses per season at the rate of 15 mg/kg each month during the RSV season. Infants born during an RSV season would require fewer.

C. Opinion of the Advisory Committee on the Use of palivizumab

Harmonizing the palivizumab immunoprophylaxis program throughout the province is clearly a major concern of the Advisory Committee. The main children's hospitals are well organized, as evidenced by the Centre mère-enfant Soleil du CHU de Québec-Université Laval's structure for managing the program. As well, the existence of clinics specializing in palivizumab administration plays a key role in optimizing prophylaxis. Discussions were held on the following elements and led to proposals.

1. The start and end dates of the RSV season should be indicated in the Héma-Québec circular. Usually, the RSV season extends from November 1 to March 31. However, in Nunavik, the RSV season is one month later in relation to that in the southern regions, that is, from December 1 to April 30.

2. Palivizumab should be administered at a maximum of 4 or 5 doses per season. This limit will depend on the prophylaxis start date corresponding to the child's situation and the end date of the RSV season. It is still too early to recommend administering only 3 doses per season, as British Columbia does in certain cases, in the absence of evidence specifically concerning Québec, because the length of the RSV season tends to increase from west to east across Canada.

   An additional dose should be administered during the RSV season to children undergoing extracorporeal blood circulation during surgery. In Feltes's study [2003], the serum palivizumab concentration in the children who received palivizumab and who underwent heart surgery decreased by more than 50%, which is below the concentration considered protective. This is why a palivizumab dose should be administered immediately after surgery, which can result in a child receiving more than 5 doses during the same RSV season. This clinical practice is essential for the immunoprophylaxis to remain optimal.

3. No palivizumab doses should be given after the set end date, except in the following special circumstances:

- If there is still strong RSV activity in Nunavik in May, one dose should be administered during this month to eligible infants who were discharged from hospital in February to April.
- For the other regions of Québec, one dose should be administered in April to certain preterm infants if there is still strong RSV activity in the community, specifically, those discharged from hospital in January to March.

This is an important recommendation if one truly wants to optimize the efficacy of this immunoprophylaxis in high-risk infants who have not received a sufficient number of doses because they were born during the RSV season. The experts pointed out that regular reports from the Institut national de santé publique du Québec (INSPQ) indicating RSV activity in the different regions are available and easily accessible. The members are of the opinion that implementing a monitoring process would not entail any major difficulties. People could identify the regions where RSV activity persists beyond the end date of the RSV season and send this information to the personnel responsible for administering palivizumab. Palivizumab's kinetics should be taken into account when deciding whether or not to authorize an additional dose, since its effect persists for up to 6 weeks. It was proposed that physicians who evaluate nonconforming cases be able to get involved in this process.

4. The dosing interval should be about 28 days.

5. To ensure the harmonization of practices pertaining to the administration of palivizumab prophylaxis at the different facilities, a provincial calendar indicating set dates should be created and included in the circular disseminated by Héma-Québec. To take into account the Holiday season, during which the risk of contagion is higher, one dose should be administered around December 15, and the first dose of the season should be administered around mid-November. These dates should be adjusted for Nunavik.

6. Clinics specializing in palivizumab administration and using a group approach with patients to minimize drug wastage should be created in Québec.

D. INESSS's recommendation

INESSS agrees with all of the proposals made by the experts consulted. It reiterates that all measures promoting the persistence of the effect of palivizumab are essential to the success of the palivizumab immunoprophylaxis program. In fact, because of the nature of this drug, its mechanism of action and its kinetics, it is crucially important that the serum palivizumab concentration be sufficient to ensure continued prophylaxis during periods of intense RSV activity. This is why INESSS once again specifically emphasizes the need to establish a provincial calendar (including an adjustment for Nunavik) and the recommendations aimed at permitting the administration of an additional dose in the special circumstances mentioned above.

As well, in its preliminary report in 2015, INESSS recommended that the MSSS put measures in place aimed at eliminating the disparities in the offer of service between the different health-care facilities, disparities that were compromising access to palivizumab. INESSS wishes to point out that since it

made this recommendation, the MSSS has taken action to correct the situation for the 2015-2016 season.

4.3 OTHER CONSIDERATIONS

The experts consulted are of the opinion that good hand hygiene at home and avoiding direct contact between high-risk children and people with RTIs are essential for preventing RSV infection.

5. REASONABLENESS OF THE PRICE

The price of a 50-mg vial of palivizumab is $752.26, while that of a 100-mg vial is $1504.51. At the rate of 15 mg/kg, the cost per dose to treat a child weighing 1 to 6.6 kg varies from $752 to $1,505. It is $2,257 for one weighing 7 to 10 kg. The calculations took drug wastage into account, based on the drug's duration of stability.

6. COST-EFFECTIVENESS

As regards pharmacoeconomics, INESSS designed a model for evaluating the cost-effectiveness of palivizumab in the different populations concerned by the recognized indications. To this end, it drew upon different validated models identified in a large number of scientific publications. Special attention was given to studies carried out in a Canadian context. However, in light of the available clinical data, this model cannot lead to any reliable conclusions for commenting on the cost-effectiveness of palivizumab administered according to the experts' recommendations. This can be explained by the weakness of the clinical evidence regarding certain populations or by the absence of evidence regarding others. In fact, the studies evaluated had many limitations, such as the absence of a control group, external validity compromised because of the care context or resource utilization, and the differences between the study populations and those to which the eligibility criteria apply. Consequently, the uncertainty regarding the data to be introduced into the pharmacoeconomic model is too great. The cost-effectiveness of palivizumab can therefore not be evaluated.

7. IMPACT ON THE HEALTH OF THE GENERAL POPULATION AND ON THE OTHER COMPONENTS OF THE HEALTH AND SOCIAL SERVICES SYSTEM, AND SPECIAL CONSIDERATIONS (HEALTH ECONOMICS, OBJECTIVE OF THE GENERAL PLAN, ETHICAL CONSIDERATIONS)

7.1 ECONOMIC ANALYSIS

Changes in Synagis® costs, the number of children treated and the mean cost per child by RSV season from 2005-2006 to 2015-2016

	05-06	06-07	07-08	08-09	09-10	10-11	11-12	12-13	13-14	14-15	15-16	Diff. 15-16 vs. 14-15
Total cost in $000s	11,954	13,136	13,409	16,270	14,173	15,639	15,757	15,486	15,955	16,816	8,910	-47.0 %
Nb of children treated	1397	1590	1595	1900	1684	1896	1828	1855	1967	1967	1270	-35.4 %
Average cost/child	$8,557	$8,262	$8,407	$8,563	$8,416	$8,248	$8,620	$8,348	$8,111	$8,549	$7,016	-17.9 %

AbbVie data, May 2016

Palivizumab costs decreased from $16.8 million in 2014-2015 to $8.9 million in 2015-2016, a decrease of 47%. The number of children treated decreased by 35%, while the average cost per child decreased by 18%. During the same period, in the rest of Canada, the number of children treated decreased as well, but only by 9.6%.

Changes in Synagis® use by the number of children treated and by RSV season from 2005-2006 to 2015-2016

Breakdown of children by palivizumab eligibility criterion

	05-06	06-07	07-08	08-09	09-10	10-11	11-12	12-13	13-14	14-15	15-16	Diff. 15-16 vs. 14-15
Chronic pulmonary disease	164	153	188	266	196	170	212	218	186	238	141	-41 %
Congenital heart disease	193	229	194	203	220	256	251	227	239	239	116	-51 %
<28 weeks	175	220	200	204	183	215	195	179	202	215	202	-6 %
29 to 32 weeks	544	601	584	731	543	614	578	621	631	589	545	-7 %
33 to 35 weeks	224	238	216	236	244	308	301	300	317	293	0	-100 %
Other: Nonconforming requests	97	149	213	260	298	333	291	310	392	393	266	-32 %
Total	1397	1590	1595	1900	1684	1896	1828	1855	1967	1967	1270	-35 %

Abbvie data, May 2016

In terms of use by category of children, the 2015-2016 criteria clearly had a major impact. No preterm infants of 33 to 35 weeks' GA received Synagis®, with the exception of a few who had one or more health problems qualifying them for a nonconforming authorization. Furthermore, the number of eligible infants with congenital heart disease fell by half because of the criterion that now limits access

to those <12 months of age as opposed to <24 months, which was the criterion in effect during the previous seasons. In addition, we note a pronounced decrease in authorizations concerning the presence of a chronic pulmonary disease or a health problem associated with severe respiratory complications (previously Criterion No. 3). This is normal, since this criterion was not very precise. It was replaced, for the 2015-2016 season, by Criteria Nos. 2, 3, 4 and 5, which are more specific to the causes of severe respiratory problems. This very likely led to a redistribution of requests between these different criteria. The number of nonconforming authorizations also decreased, because many of these requests concerned health problems that are now covered by the new Criteria Nos. 3, 4 and 5, which no longer indicate the systematic need for oxygen therapy (cystic fibrosis, neuromuscular disorders or congenital airway anomalies). The number of cases concerned is 150.

Lastly, the number of requests turned down in 2015-2016 was 50, which is almost the same number as in 2014-2015 (n = 45). Of the 50 requests rejected, 28 concerned children over 24 months of age.

7.2 CHALLENGES ASSOCIATED WITH COMPLIANCE WITH THE DETAILS OF ADMINISTRATION

When mention is made of the optimal use of palivizumab, it is natural to ask about the types of target populations, that is, those that could derive the greatest therapeutic benefit from it. The details of administration often take second place, yet they are of paramount importance. In fact, preventing severe infections also depends on the precautions taken to ensure the maintenance of a sufficient and stable plasma antibody concentration. This is why instituting a provincial calendar, with an adjustment for Nunavik, to standardize practices pertaining to the administration of palivizumab doses is so important. Furthermore, if the criteria concerning the administration of additional doses are not spelled out in the circular, all previously taken precautions could be in vain, since the risk of an RSV infection worsening to the point where the child requires hospitalization increases if these criteria are not met.

7.3 CHALLENGES ASSOCIATED WITH VALUES

The following items should be considered when developing recommendations: the vulnerability of the target population; parental anxiety associated with a child's hospitalization, which is sometimes prolonged after birth; and, lastly, the risks and drawbacks of hospitalization for the child and his/her family. Furthermore, INESSS's recommendations should also take into account the costs considered acceptable in similar situations, while at the same time taking into consideration the problem of risk management in a vulnerable population in a context of significant uncertainty regarding the therapeutic value of using palivizumab prophylaxis in certain pediatric populations. This is a special case where it is reasonable to accord decisive weight to the consensus of the experts consulted. It will be noted that the Advisory Committee took into account a systematic literature review, at the end of which it felt that the external validity of the major studies, which were considered to be of good methodological quality and of a high level of evidence, is now diminished because of advances in medical care for the infants and young children targeted by this type of immunoprophylaxis. The evaluation of the ethical considerations also took into account the initiative by a member of the expert committee to collect data at a pediatric tertiary care centre where he practices, in order to assess the impact of revoking the eligibility criteria concerning preterm infants of 33 to 35 weeks' GA. A decrease,

even a small one, in the uncertainty is considerable in circumstances where it is not realistic to count on the publication of new data from studies of high methodological quality.

7.4 PROCEDURAL ETHICS CONSIDERATIONS

In light of Chang's [2016] and Mitchell's [2015] criticisms about the potentially undue influence of economic concerns on the drafting of the CPS's recent guidelines, it seemed to be a priority to carry out the assessment process in such a way that the reservations regarding the drug's cost would not influence the evaluation of its therapeutic value. Furthermore, prior knowledge of the issue suggested that the experts' opinion would be key to developing the recommendations. Therefore, special care was taken when forming the Advisory Committee on the Use of Palivizumab in terms of specialties and practice settings.

8. CONCLUSION

Upon continuing its assessment activity in 2016, INESSS realized that the assessment method that it usually uses for drugs to be entered on the lists of medications poses challenges when applied to a prophylactic drug like palivizumab. It was found that the studies of high quality and of a high level of evidence are scarce and were carried out many years ago, with the result that their external validity is compromised. The rest of the literature consists only of numerous observational studies, which, for the most part, were of low methodological quality. Furthermore, the use of palivizumab is not documented in certain pediatric populations considered at risk for severe RSV infection and for which nonconforming authorizations had been granted. Lastly, it is unlikely that good studies aimed at comparing the effect of palivizumab with that of placebo will eventually be conducted in the short or medium term in these vulnerable, low-prevalence groups. This said, INESSS concluded that it was nearly impossible to assess the merits of using palivizumab in the different populations identified, using a strictly evidence-based approach, as it generally recommends. This is why, in certain situations, it accorded significant weight to the opinion of the specialized experts on the Advisory Committee on the Use of Palivizumab and the opinions of the learned societies. This was an exceptional and circumstantial approach.

To conclude, in its final recommendations summarized at the beginning of this report, INESSS would like to emphasize the following points:

- The revocation of the criterion concerning preterm infants born at 33 to 35 6/7 weeks' gestation did not, on the face of it, seem to have had any clinically significant consequences in this population compared to the general pediatric population, either in terms of the number of hospitalizations or the degree of damage, during the 2015-2016 RSV season. However, INESSS feels that it is imperative to evaluate the consequences of revoking this criterion over several years because the characteristics of RSV seasons vary over time. For instance, the last season was marked by a particular set of dynamics, namely, a late start of the infection period and a high prevalence of the influenza type B virus.

- INESSS believes that the organization of palivizumab immunoprophylaxis and of the care provided to Nunavik infants is adequate to ensure the proper application of its recommendations regarding term and preterm infants. These infants are highly vulnerable because they have several risk factors for severe RSV infection that are clearly recognized worldwide. They are unquestionably among the populations most at risk in Québec. Furthermore, given the community experience of residents of the Far North and their perceptions of the serious infections that have decimated their people in the past, INESSS feels that these communities will be engaged in an immunoprophylaxis program.
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- INESSS emphasizes applying all the recommended measures aimed at prolonging palivizumab's effect. Indeed, maintaining a high enough serum palivizumab concentration to ensure ongoing prophylaxis during periods of intense RSV activity is the key to the success of an immunoprophylaxis program. Therefore, there is a need for an administration schedule and to authorize an additional dose in the special circumstances mentioned above.
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- Although it was, in the past, unusual to include exclusion criteria in the circular for the immunoprophylaxis program in the past, INESSS believes that this approach should now be adopted to limit the pointless submission of nonconforming requests.
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- Putting in place structured, independent monitoring of the consequences of the new recommendations is a must. Given the economic burden associated with the complications of RSV respiratory tract infections and with immunoprophylaxis, INESSS believes that it is now essential to maintain a registry, which could be modelled after those maintained by other Canadian provinces. The difficulties encountered in evaluating the efficiency of palivizumab are due, in large part, to the absence of contemporary comparative data for Québec.

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D'autres références, publiées ou non publiées, ont été consultées.

APPENDIX I

Revue systématique – Institut national d'excellence en santé et en services sociaux (INESSS). Effet du palivizumab en prophylaxie sur la diminution des complications associées au virus respiratoire syncytial chez les enfants : revue systématique. Rapport rédigé par Marie-Claude Breton, Michel Rossignol, Mélanie Tardif, Alvine K. Fansi et Cédric Jehanno. Québec, Qc : INESSS; 2016.

APPENDIX II

Membres du Comité consultatif sur l'usage du palivizumab

Président du comité

Dr Stéphane P. Ahern, interniste-intensiviste, Hôpital Maisonneuve-Rosemont, président du Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription (CSEMI) de l'INESSS

Experts cliniciens externes

Dre Valérie Bertelle, pédiatre néonatalogie, Centre Hospitalier Universitaire (CHU) de Sherbrooke (en 2015 seulement)
Dr François Boucher, pédiatre infectiologue, CHU de Québec-Université Laval
Dr Georges Caouette, pédiatre néonatalogie, CHU de Québec-Université Laval
Dr Patrick Daigneault, pneumologue pédiatre, CHU de Québec-Université Laval
Dre Anne Fournier, cardiologue pédiatre, CHU Ste-Justine
Dr Arnaud Gagneur, pédiatre néonatalogiste, CHU de Sherbrooke (en 2016 seulement)
Dr Marc Lebel, pédiatre infectiologue, CHU Ste-Justine
Dr Jacques-Édouard Marcotte, pneumologue pédiatre, CHU Ste-Justine
Dre Johanne Morel, pédiatre, CHU McGill (consultée par téléphone relativement aux enfants des collectivités éloignées en 2016 seulement)
Dr Jesse Papenburg, pédiatre infectiologue, Hôpital de Montréal pour enfants
Dr Charles Rohlicek, cardiologue pédiatre, Hôpital de Montréal pour enfants

Membres experts du CSEMI

M. Bernard Keating, éthicien
Dr Richard Lalonde, interniste-infectiologue, Hôpital Royal Victoria (en 2015 seulement)

Membres de l'INESSS (non-votants)

Mme Marie-Claude Aubin, Ph. D., coordonnatrice en pharmacoéconomie, Direction du médicament (DM)
M. Julien Baril, économiste, DM
Mme Johanne Lachance, pharmacienne, professionnelle en pharmacothérapie, DM
Mme Anne-Marie Lemieux, B. Sc., M. Sc., professionnelle en pharmacothérapie, DM
Mme Carole Marcotte, B. Pharm., directrice, Direction de l'évaluation des médicaments aux fins d'inscription (DEMFI) (en 2015 seulement)
Mme Geneviève Martin, Ph. D., professionnelle scientifique en santé, Direction de la biologie médicale (en 2015 seulement)

Invité (non votant)

Dr Michel Rossignol, MD, M. Sc. FRCPC, conseiller médical, DM (en 2016 seulement)

APPENDIX III

Résumé des critères d'admissibilité des programmes d'immunoprophylaxie par le palivizumab en vigueur au Canada[a] pour la saison du VRS 2015-2016

Populations	Québec	Colombie-Britannique	Alberta	Saskatchewan	Manitoba	Ontario	Nouveau-Brunswick	Nouvelle-Écosse	Île-du-Prince-Édouard	Terre-Neuve-et-Labrador	Territoire du Nunavut	Territoires du Nord Ouest[b]	Territoire du Yukon
Bébés prématurés	AG <33 semaines + Âgés < 6 mois en début de saison	AG < 29 semaines + Retour à domicile après la naissance ≥ 2015-09-01 AG de 29 à 34 $^{6/7}$ semaines, sans BDP + Retour à domicile après la naissance ≥ 2015-10-01 + Score ≥ 42 points, calculé avec l'outil d'évaluation des risques[c] d'infection grave[b]	AG ≤ 32 $^{6/7}$ semaines + Nés > 2015-05-21 + Âge < 6 mois au 2015-12-01 AG de 33 $^{0/7}$ à- 35 $^{6/7}$ semaines + Nés > 2015-10-31 + Score > 55 points, calculé avec l'outil d'évaluation des risques d'infection grave[c]	AG ≤ 32 $^{6/7}$ semaines + Âge ≤ 6 mois au début de la saison AG de 33 $^{0/7}$ à 35 $^{6/7}$ semaines + Nés durant la saison du VRS en cours + Score ≥ 60 points, calculé avec l'outil d'évaluation des risques d'infection grave[c]	AG < 33 semaines + Âge < 6 mois au début de la saison AG de 33 à 35 semaines + Facteurs de risque suffisants (pas de renseignement sur le score minimal requis calculé avec l'outil d'évaluation des risques d'infection grave[c])	AG ≤ 32 semaines + Âge < 6 mois au début de la saison ou durant celle-ci AG de 33 à 35 semaines + Âge < 6 mois au début de la saison ou durant celle-ci + Non-résidents d'une collectivité isolée + Score ≥ 49 points, calculé avec l'outil d'évaluation des risques d'infection grave[c]	AG ≤ 32 $^{6/7}$ semaines + Âge < 6 mois au début de la saison AG de 33 à 35 semaines + Âge < 6 mois au début de la saison ou durant celle-ci + Score ≥ 49 points, calculé avec l'outil d'évaluation des risques d'infection grave[c]	AG ≤ 32 $^{0/7}$ semaines + Âge ≤ 6 mois au début de la saison AG de 32 $^{1/7}$ à 35 $^{6/7}$ semaines + Âge ≤ 6 mois au début de saison ou durant celle-ci + Score ≥ 65 points, calculé avec l'outil d'évaluation des risques d'infection grave[c] **Cas par cas** Si score de 49 à 64 points	AG ≤ 32 $^{0/7}$ semaines + Âge ≤ 6 mois au début de la saison AG de 32 $^{1/7}$ à 35 $^{6/7}$ semaines + Âge ≤ 6 mois au début de saison ou durant celle-ci + Score ≥ 65 points, calculé avec l'outil d'évaluation des risques d'infection grave[c] **Cas par cas** Si score de 49 à 64 points	AG ≤ 32 semaines + Âge ≤ 6 mois au début de la saison	AG ≤ 35 $^{6/7}$ semaines + Âge ≤ 6 mois au début de la saison	AG < 32 $^{6/7}$ semaines + Nés > 2014-05-31 AG de 33 $^{0/7}$ à 35 $^{6/7}$ semaines + Nés > 2014-10-31 + Facteurs de risque (pas de renseignement sur le score minimal requis calculé avec l'outil d'évaluation des risques d'infection grave[c])	AG < 29 $^{0/7}$ semaines + Retour à domicile après la naissance ≥ 2015-09-01 AG de 29 $^{0/7}$ à 34 $^{6/7}$ semaines + Retour à domicile après la naissance ≥ 2015-10-01 + Score > 41 points, calculé avec l'outil d'évaluation des risques d'infection grave[c]
Enfants atteints de BDP ou d'une MPC	Âge < 24 mois en début de saison + BPD[d] ou MPC du nouveau-né[e] + besoin persistant en O_2 < 6 mois avant la saison ou pendant celle-ci	Ex-prématurés Âge ≤ 12 mois au début de la saison + BDP/MCP[f] + Besoin continu en O_2 ≥ 2015-07-01 dû à la MPC[g] **Cas par cas** Nés ≥ 2013-11-01 et BDP grave	Ex-prématuré AG ≤ 35 6/7 semaines + Âge < 24 mois au 2015-12-01 + MPC + Besoin en O_2 à domicile > 2015-05-31 ou Besoin à long terme d'un traitement ou Exacerbation respiratoire ayant nécessité des stéroïdes systémiques	Âge ≤ 24 mois au début de saison + BDP/MPC + Besoin d'O_2 ≤ 6 mois avant le début de la saison	Âge ≤ 24 mois au début de la saison + BDP + Besoin d'O_2 ≤ 6 mois avant le début de la saison	Âge < 24 mois au début de la saison + BDP/MPC + Besoin d'O_2 ou d'une thérapie médicale < 6 mois avant le début de la saison	Âge ≤ 24 mois au début de la saison + BDP/MPC + Besoin d'O_2 ou d'une thérapie médicale < 6 mois avant le début de la saison	Âge < 24 mois au début de la saison + BDP/MPC + Besoin d'O_2 ou d'une thérapie médicale < 6 mois avant le début de la saison	Âge < 24 mois au début de la saison + BDP/MPC + Besoin d'O_2 ou d'une thérapie médicale < 6 mois avant le début de la saison	Âge ≤ 24 mois au début de la saison + BDP/MPC + Besoin d'O_2 < 6 mois avant le début de la saison	Âge < 12 mois au début de la saison + MPC de la prématurité + Besoin d'O_2 durant la saison ou Traitement médicamenteux (diurétiques, bronchodilatateurs ou stéroïdes) _____ Âge < 24 mois au début de la saison + BDP/MPC de la prématurité + Besoin d'O_2 durant la saison ou le sevrage de l'O_2 a eu lieu < 3 mois avant le début de la saison	Ex-prématurés AG ≤ 35 $^{6/7}$ semaine + Âge < 24 mois au 2014-12-01 + MPC définie par un besoin d'O_2 à domicile > 2014-05-31	Âge ≤ 12 mois au début de la saison + BDP/MPC + Besoin d'O_2 ≥ 2015-07-01 _____ **Cas par cas** Âge ≤ 24 mois au début de la saison + BDP grave

Populations	Québec	Colombie-Britannique	Alberta	Saskatchewan	Manitoba	Ontario	Nouveau-Brunswick	Nouvelle-Écosse	Île-du-Prince-Édouard	Terre-Neuve-et-Labrador	Territoire du Nunavut	Territoires du Nord Ouest[b]	Territoire du Yukon
Enfants atteints de fibrose kystique	Âge < 24 mois au début de la saison + symptômes respiratoires ou retard de croissance significatif	**Cas par cas** Nés ≥ 2013-11-01 + maladie symptomatique	Âge < 24 mois au 2015-12-01	Âge ≤ 12 mois au début de la saison	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Cas par cas Si <12 mois	Cas par cas	Cas par cas	Cas par cas	Cas par cas Âge < 24 mois au début de la saison + Besoin en O_2 à domicile ou Antécédent d'hospitalisation de longue durée en raison d'une maladie pulmonaire grave ou Immunodépression grave	Âge < 24 mois au 2014-12-01	**Cas par cas** Né ≥ 2013-11-01 + Maladie symptomatique
Enfants atteints de troubles neuromusculaires	Âge < 24 mois au début de la saison + troubles neuromusculaires entravant l'évacuation des sécrétions des voies aériennes de façon importante	**Cas par cas** Âge ≤ 24 mois au début de la saison + maladie neuromusculaire progressive empêchant l'évacuation des sécrétions	Amyotrophie spinale de type I si le poids est < 15 kg (pas de restriction sur l'âge)	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	**Cas par cas** Âge ≤ 24 mois au début de la saison + Maladie neuromusculaire progressive empêchant l'évacuation des sécrétions
Enfants présentant une anomalie congénitale des voies respiratoires	Âge < 24 mois au début de la saison + Anomalies congénitales des voies respiratoires supérieures entravant l'évacuation des sécrétions des voies aériennes de façon importante	Aucun renseignement particulier disponible	Âge < 24 mois au 2015-12-01 + Anomalie congénitale des voies respiratoires, telle une fistule trachéo-œsophagienne	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	**Cas par cas** Âge < 24 mois au début de la saison + Obstruction des voies aériennes supérieures + Besoin en O_2 à domicile ou Antécédent d'hospitalisation de longue durée en raison d'une maladie pulmonaire grave ou Immunodépression grave	Aucun renseignement particulier disponible	Aucun renseignement particulier disponibl
Enfants atteints d'une maladie cardiaque ou cardio-pulmonaire	Âge < 12 mois au début de la saison + cardiopathie congénitale, cardiomyopathie, myocardite importantes du point de vue hémodynamique ou HTP modérée ou grave (Demande soumise par un cardiologue pédiatrique) **Cas par cas** Handicap cardiorespiratoire sévère + Si né ≥ 1er nov. 2013	Âge < 12 mois au début de la saison + Maladie cardiaque congénitale aux conséquences hémodynamiques significatives (Demande soumise par un cardiologue pédiatrique) **Cas par cas** Nés ≥ 2013-11-01 + HTP ou autres problèmes cardio-pulmonaires graves	Âge < 24 mois au 2015-12-01 + Maladie cardiaque congénitale ayant des conséquences hémodynamiques graves (liste fournie) (Demande soumise par un cardiologue pédiatrique)	Âge ≤ 24 mois au début de saison + Maladie cardiaque congénitale cyanogène ou non cyanogène, ayant des conséquences hémodynamiques importantes + nécessitant une chirurgie correctrice ou un traitement médicamenteux	Âge < 24 mois au début de la saison + Maladie cardiaque importante du point de vue hémodynamique (Demande soumise par un cardiologue pédiatrique)	Âge < 24 mois au début de la saison + Maladie cardiaque congénitale cyanogène ou non cyanogène, ayant des conséquences hémodynamiques importantes + nécessitant une chirurgie correctrice ou un traitement médicamenteux	Âge < 24 mois au début de la saison + Maladie cardiaque congénitale cyanogène ou non cyanogène, ayant des conséquences hémodynamiques importantes + nécessitant une chirurgie correctrice ou un traitement médicamenteux	Âge < 24 mois au début de la saison + Maladie cardiaque importante du point de vue hémodynamique (HTP, insuffisance cardiaque congestive, maladie cardiaque cyanogène ou autre maladie cardiaque)	Âge < 24 mois au début de la saison + Maladie cardiaque importante du point de vue hémodynamique (HTP, insuffisance cardiaque congestive, maladie cardiaque cyanogène ou autre maladie cardiaque)	Âge ≤ 24 mois au début de la saison + Maladie cardiaque congénitale cyanogène ou non cyanogène, ayant des conséquences hémodynamiques importantes + nécessitant une chirurgie correctrice ou un traitement médicamenteux	Âge < 12 mois au début de la saison + Maladie cardiaque importante du point de vue hémodynamique + nécessitant une chirurgie correctrice ou un traitement médicamenteux (diurétiques, bronchodilatateurs ou stéroïdes)	Nés > 2012-11-30 + Maladie cardiaque importante du point de vue hémodynamique	Âge ≤ 12 mois au début de la saison + Maladie cardiaque chronique ayant des conséquences hémodynamiques importantes (Approbation du cardiologue) **Cas par cas** Nés ≥ 2013-11-01 + HTP

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Enfants immunodéprimés	Âge <24 mois au début de la saison + Transplantation du cœur, du foie ou du poumon ou Greffe de cellules souches et Survenues < 6 mois avant le début de la saison	**Cas par cas** Âge ≤ 12 mois au début de la saison + Immunodéficience grave (greffe de cellules souches, LLA, AML, DCIS, protocole ICE, protocole pour tumeur cérébrale invasive)	Âge < 24 mois au 2015-12-01 et Greffe de cellule souche ou Immunodéficience significative	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	**Cas par cas** Âge < 24 mois au début de la saison + Immunodépression grave + Besoin en O_2 à domicile ou Antécédent d'hospitalisation de longue durée en raison d'une maladie pulmonaire grave	Âge < 24 mois au 2014-12-01 + Immunodéficience grave	**Cas par cas** Âge ≤ 24 mois au début de la saison + Immunodéficience grave (exemple : greffe de cellules souches)
Enfants résidant dans une collectivité isolée	Non admissibles sauf si répond aux autres critères	Pas de critère particulier, mais l'outil d'évaluation des risques d'infection grave[c] prend en considération un lieu de résidence situé dans une région éloignée, soit à plus d'une heure de route ou à plus de 100 km du l'hôpital le plus près	Pas de critère particulier, mais l'outil d'évaluation des risques d'infection grave[c] prend en considération un lieu de résidence situé à plus de 2 heures de route de l'hôpital le plus près qui fournit les soins requis pour une bronchiolite	Prématurés AG de 33 $^{0/7}$ à 35 $^{6/7}$ semaines + Résidant à La Ronge ou au nord de cette ville	AG de 33 $^{0/7}$ à 35 $^{0/7}$ semaines + Résident d'une collectivité éloignée du Nord	AG de 33 semaines à 35 semaines + Âge < 6 mois au début de la saison ou durant celle-ci + Résident d'une collectivité isolée où un hôpital fournissant des soins pédiatriques n'est pas facilement accessible et qui oblige un transport par ambulance pour y être admis.	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	AG ≤ 35 semaines + Âge < 6 mois au début de la saison + Résidents d'une collectivité nordique, isolée ou éloignée, **selon une évaluation** de la facilité d'accès aux soins médicaux et d'autres facteurs connus pour augmenter le risque de complications de l'infection	Aucun renseignement particulier disponible	Pas de critère particulier, mais un lieu de résidence situé à au moins 1 heure de route d'un hôpital offrant un traitement de la bronchiolite est l'un des facteurs pris en compte par l'outil d'évaluation des risques d'infection grave[c].	L'ensemble du territoire du Yukon est considéré comme une région éloignée. L'outil d'évaluation des risques d'infection grave[c] en tient compte.
Enfant en santé issu d'une naissance multiple dont le jumeau est admissible au palivizumab	Inadmissible	Âge < 12 mois au début de la saison + Né à < 35 semaines d'AG, autrement en bonne santé	AG de 33 $^{0/7}$ à 35 $^{6/7}$ semaines, autrement en bonne santé	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Enfant en santé issu d'une naissance multiple dont le jumeau est admissible au palivizumab	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Enfant en santé issu d'une naissance multiple dont le jumeau est admissible au palivizumab	AG < 34 $^{6/7}$ semaines, autrement en bonne santé, + Quittant l'hôpital pour la 1re fois
Enfants atteints du syndrome de Down	Inadmissible, sauf si répond aux autres critères	Cas par cas Enfants sans maladie cardiaque importante + retour à domicile ≥ 2015-09-01 + facteurs de risque (score minimal calculé avec l'outil d'évaluation du risque d'infection grave[c] non indiqué)	Âge < 12 mois au 2015-12-01	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Âge < 24 mois au début de la saison + Atteints ou non d'une maladie cardiaque congénitale	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	**Cas par cas** Âge < 24 mois au début de la saison + Besoin en O_2 à domicile ou Antécédent d'hospitalisation de longue durée en raison d'une maladie pulmonaire grave ou Immunodépression grave	Âge ≤ 12 mois au 2014-12-01	**Cas par cas** Né ≥ 2015-09-01 + Sans maladie cardiaque importante du point de vue hémodynamique + Facteurs de risque (score minimal calculé avec l'outil d'évaluation des risques[c] d'infection grave non indiqué)
Enfants ayant besoin d'une aide respiratoire	Aucun renseignement particulier disponible	Âge < 24 mois au début de la saison + Besoin d'aide respiratoire à domicile (trachéotomie, O_2 ou CPAP) ≥ 2015-11-01	Âge < 24 mois au 2015-12-01 + Trachéotomie ou Besoin d'O_2 à domicile ou Aspiration méconiale avec besoin d'O_2 à domicile ou Reflux œsophagien	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Aucun renseignement particulier disponible	Âge ≤ 24 mois au début de la saison + Besoin d'aide respiratoire ≥ 2015-11-0 (trachéotomie, O_2 en continu ou ventilation)

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			avec besoin d'O_2 à long terme **Exclusion :** Apnée centrale requérant O_2										
Enfants présentant d'autres problèmes de santé	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Âge < 24 mois au 2015-12-01 + Hernie diaphragmatique avec ou sans besoin d'O_2 ou Autres maladies pulmonaires graves Rien n'exclut la possibilité d'une évaluation au cas par cas dans d'autres situations	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Rien n'exclut la possibilité d'une évaluation au cas par cas.	Rien n'exclut la possibilité d'une évaluation au cas par cas.	**Cas par cas** Âge < 24 mois au début de la saison + Maladie pulmonaire chronique autre que la MPC + Besoin en O_2 à domicile ou Antécédent d'hospitalisation de longue durée en raison d'une maladie pulmonaire grave ou Immunodépression grave Rien n'exclut la possibilité d'une évaluation au cas par cas.	Âge < 24 mois au 2014-12-01 + Problèmes respiratoire graves Rien n'exclut la possibilité d'une évaluation au cas par cas dans d'autres situations.	**Cas par Cas** Âge ≤ 24 mois au début de la saison + Malformation pulmonaire Rien n'exclut la possibilité d'une évaluation au cas par cas dans d'autres situations.

a Les renseignements présents dans ce tableau proviennent de documents trouvés sur le Web ou fournis par le fabricant du palivizumab. En cas de disparité avec les documents officiels de chaque province ou territoire canadiens, ces derniers prévalent.
b La seule information trouvée concerne les critères en vigueur pour la saison du VRS 2014-2015.
c Les outils d'évaluation des risques d'infection grave par le VRS pouvant conduire à une hospitalisation peuvent différer selon la province ou le territoire.
d La BDP est définie par un besoin en oxygène persistant chez un bébé prématuré après 28 jours de vie et ayant atteint au moins 36 semaines d'âge gestationnel, en plus de présenter une histoire caractéristique de la maladie.
e La MPC du nouveau-né est définie par un besoin en oxygène persistant chez un nouveau-né à perme ou près du terme en raison d'une condition pulmonaire chronique non spécifiée dans les autres critères.
f La BDP/MCP est définie par un besoin continu en oxygène ou de ventilation par pression positive continue après 28 jours de vie.
g LA MPC est définie par une dépendance à l'oxygène ou à la CPAP, après 28 jours de vie ou à un âge corrigé de 36 semaines.
AG Âge gestationnel
CPAP Ventilation par pression positive continue
DCIS Déficit immunitaire combiné sévère
HTP Hypertension pulmonaire
ICE Isofosfamide/étoposide, carboplatine et étoposide, donnés dans l'ordre sur 3 jours, pour le traitement de la maladie de Hodgkin
LLA Leucémie lymphoblastique aigüe
LMA Leucémie myéloïde aigüe
O_2 Oxygène