STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3	A population-based matched cohort study identified children <24 months with and without hospitalized RSV in 2006-2016.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	A cost-of-illness analysis was performed using linked administrative health data, with subjects stratified by gestational age and congenital heart disease, and propensity score-matched on established risk factors. The principal outcome was attributable healthcare costs per case, reflecting the difference in direct medical costs between the groups, calculated to 12 months post-discharge
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Decision-makers require accurate estimates of costs attributable to disease to inform what prevention and treatments are economically viable. Operational decisions around RSV prevention and treatment programs, including novel vaccines, expanded palivizumab administration, or targeted behavioral modification to high-risk groups, are impacted by baseline data on disease costs.
Objectives	3	State specific objectives, including any prespecified hypotheses	4	The objective of this cost-of-illness study is to estimate the healthcare costs attributable to hospitalized RSV illness among infants and young children in Ontario, Canada from the healthcare payer perspective.
Methods				
Study design	4	Present key elements of study design early in the paper	5	We conducted a population-based, retrospective matched cohort study of all children less than age 24 months in Ontario, Canada, to estimate the attributable healthcare costs of severe RSV.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	Our study was based on routinely collected administrative health databases housed at ICES Children born between April 1, 2006 and March 31, 2016 were identified and included if covered continuously by the provincial health insurance plan from birth until three years of age

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	Children born between April 1, 2006 and March 31, 2016 were identified and included if covered continuously by the provincial health insurance plan from birth until three years of age
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6	Once stratified into these subgroups, cases were matched with up to five controls on birth month, year, and propensity score, using a caliper of 0.2 SD.22 A propensity score was employed to balance covariates between cases and controls to minimize bias when calculating attributable costs
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	The primary outcome was attributable healthcare costs per child hospitalized with RSV over a 12-month period. The analysis was performed from the perspective of the public healthcare payer and included direct medical costs borne to the Ministry of Health and Long-Term Care. We used a person-level costing algorithm developed and validated based on Ontario health administrative data
			7	Difference in mean total costs between matched RSV-infected cases and controls was operationalized as attributable to RSV, assuming all other factors being equal from the propensity score matching process.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5	The primary exposure was hospitalization for severe RSV illness. Episodes were identified from the Discharge Abstract Database, compiled by the Canadian Institute for Health Information, using a validated algorithm of RSV-related ICD-10 codes
Bias	9	Describe any efforts to address potential sources of bias		

Study size	10	Explain how the study size was arrived at	5	Children born between April 1, 2006 and March 31, 2016 were identified and included if covered continuously by the provincial health insurance plan from birth until three years of age

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6	A propensity score was employed to balance covariates between cases and controls to minimize bias when calculating attributable costs, and included: sex, regional health network, rurality, income quintile, maternal age, size for gestational age, birth order, twin status, chronic lung disease, Trisomy 21, and Complex Chronic Condition (CCC) categories.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6	To minimize potential unmeasured confounding factors, RSV-infected cases and controls were initially stratified by the presence of major risk factors: hemodynamically significant congenital heart disease (CHD) and gestational age (GA) groups using published algorithms of diagnostic codes
		(*b*) Describe any methods used to examine subgroups and interactions	6	Once stratified into these subgroups, cases were matched with up to five controls on birth month, year, and propensity score, using a caliper of 0.2 SD
		(*c*) Explain how missing data were addressed	5-6	As it was not possible to calculate attributable costs for RSV cases who died within a year of their index date (defined below), cumulative costs were reported for this group
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5	included if covered continuously by the provincial health insurance plan from birth until three years of age
		(*e*) Describe any sensitivity analyses		n/a
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7	During the study period, 1,340,330 children were born in Ontario, from which were identified 14,790 cases of hospitalized RSV.
		(b) Give reasons for non-participation at each stage	7	Twenty cases died during hospitalization and another 31 died within the follow-up period. There were 145 (<1%) cases and 18,084 (1.5%) controls excluded from the cohort because they did not have provincial

				health insurance coverage for the full 12 months following their RSV-related admission.
			8	Of the eligible cases, 131 (0.9%) were unable to be matched with at least one control and excluded from the cost analysis. After applying exclusion criteria and propensity score matching, the final cohort size was 14,608 RSV-infected cases with 72,040 matched RSV-unexposed controls
		(c) Consider use of a flow diagram	-	Figure 1 (figures document)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	-	Table S5 (supplemental tables document)
		(b) Indicate number of participants with missing data for each variable of interest	-	Tables S4, S5 (supplemental tables document)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7	coverage for the full 12 months following their RSV-related admission
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8	Mean costs per case of RSV requiring hospitalization was C$11,502 (SD=26,885) compared to C$2,292 (SD=15,529) for matched controls
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-	Table 1 (document)
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8	Figure 2 illustrates the cost distribution per individual, demonstrating higher expenditure in cases compared to matched controls All cost categories were significantly higher ($p<0.001$) for cases compared with controls (Figure S4), with the major difference driven by costs during the index hospitalization. RSV-infected cases also had higher costs due to physician billings and ED visits in the period leading up to and including hospitalization
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	The mean attributable cost per case of hospitalized RSV was C$8,797 (95% CI: 8,375-9,224). Higher costs per case were observed in high-risk groups, particularly among children with hemodynamically significant heart disease; however the greatest burden was among infants between 36 and 43 weeks GA at an average annual cost of C$11.2 million.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	The average annual cost of hospitalized RSV, at C$12.9 million, is likely a conservative estimate. Our analysis excluded RSV-related deaths and RSV cases with multiple co-morbidities who could not be matched to RSV-nonexposed controls; these groups had significant overall costs of care. Second, it was not possible to estimate additional costs of outpatient physician or ED visits for mild-to-moderate RSV as there is no validated algorithm to identify this patient cohort, despite nearly 20% of infants accessing urgent care. Moreover, a recent study demonstrated increased healthcare resource utilization for 5 years following infant RSV infection compared to healthy controls, although the greatest difference in burden was in the first 2 years. Finally, we were unable to include patient out-of-pocket costs, including caregiver time, loss of productivity and transportation, the latter of which is a significant driver of costs in remote Canadian communities.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14	Our study examined the attributable incident costs of severe RSV disease in a large, rigorously matched cohort of infants and young children in Ontario, Canada. At an attributable cost of C$8,797 per case, this cost-of-illness analysis provides much-needed data on direct healthcare costs

				attributable to hospitalized RSV in the largest published cohort of children under 2 years.
Generalisability	21	Discuss the generalisability (external validity) of the study results	14	our data will enable decision-makers in a public payer system to compare new interventions
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2	BDK receives support from the Ontario Child Health Support Unit, which is funded by the Ontario SPOR SUPPORT Unit and supported by the Canadian Institutes of Health Research and the Province of Ontario, which had no role in the study design, collection, analysis and interpretation of the data, writing of the report or decision to submit the manuscript for publication.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.