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ORIGINAL ARTICLE

Global prevalence of infections in newborns with respiratory complications: systematic review and meta-analysis

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ABSTRACT

Background and Objectives: Newborns as a vulnerable population are exposed to congenital and acquired infections during and after birth. There are several reports of the isolation and reporting of infectious agents (IAs) in early life of newborns with respiratory manifestations, and the present comprehensive study provides a snapshot of the current global situation of the prevalence of IAs in newborns with respiratory symptoms.

Materials and Methods: A systematic search was conducted in main databases, including PubMed, Scopus, Web of science, and Google scholar. The pooled prevalence of infectious agents (IAs) in newborns was estimated using comprehensive meta-analysis software based on random effects model.

Results: Out of 44 inclusive studies (50 datasets) for IAs in newborns, the pooled prevalence was estimated to be 12.2% (95% CI: 6.40-22.0%) and the highest and lowest prevalence of IAs was related to the Brazil (78.2%, 95% CI: 31.0-96.6%), and UK (0.01%, 95% CI 0.01-0.01%) respectively.

Conclusion: The high prevalence of IAs in newborns emphasizes considers the necessary measures to prevent respiratory infections.

Keywords: Newborn; Communicable diseases; Infections; Respiratory tract diseases; Meta-analysis

INTRODUCTION

Common respiratory disorders in newborns include a wide range of congenital complications to acquired disorders, which is very important due to the sensitivity of the respiratory system (1). Respiratory distresses, malfunctioning of the lungs or cardiovascular system, fluid retention in the lungs are among the complaints that are reported in abundance annually (1). Respiratory complications caused by respiratory infections (RIs) are common in the first month after the birth of offspring and can be life-threatening if not treated properly. RIs are mostly caused by viruses and bacteria and less by fungi and parasites (2). In this regard, acquisition of RIs in newborns occurs in the uterine cavity in the face of maternal flora or after birth and with environmental factors such as hospital or household agents (3). RIs caused by infectious microorganisms such as *Streptococcus* (group B), *Ureaplasma* spp. and respiratory syncytial viruses (RSV), influenza and para-influenza, as well as rhinovirus are among the most prevalent cases reported in newborns (4). Among these, viruses have a great correspondence in RIs, so that they were probably more prevalent before, but the lack of proper diagnostic methods has prevented their detection and reporting (5). Nowadays, with the development of molecular methods with high sensitivity and spec-

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ificity, the identification of viruses has been facilitated. In recent years, with the emergence of the SARS-Co-2 virus pandemic, the shift of respiratory diseases has been towards the infection caused by this virus, namely, COVID-19; with the possibility of vertical transmission from mother to fetus has been raised in this virus as well as in other organisms (6). It should be noted that in recent years, the global prevalence of other RIs has decreased due to preventive measures for COVID-19 (7). Preventive measures such as vaccination programs for mothers and newborns prevent the incidence and progress of respiratory diseases. But has it been successful in preventing respiratory infectious agents (IAs)? To answer this question, investigations are still ongoing. Up to now, no inclusive report of the prevalence and/or the frequency of isolated infectious agents from newborns is available; hence, the present review, with a focus on RIs, has attempted to provide a unique and comprehensive picture of the global prevalence of respiratory infections in newborns.

MATERIALS AND METHODS

In the systematic review and meta-analysis that follows the instructions below Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (8). To assess the association of and prevalence IAs with or without respiratory symptoms, we conducted a systematic review through which all studies were searched by two independent reviewers in several electronic databases including PubMed, Web of Science, Scopus and Google scholar from 2000 to 2023. The following combinations of keywords were used from medical topics: “Respiratory Infections” OR “Infectious Agents” OR “Infections” AND “prevalence” OR “epidemiology” AND “Newborns” OR “Infants” AND “Respiratory disorder” OR “Respiratory complications”. The reference lists in the relevant studies were also reviewed.

Inclusion and exclusion criteria. The inclusion criteria for eligible Studies were as follows: (a) All observational studies (case–control, cohort, and cross-sectional design); (b) Published: Jan, 1, 2000 to Aug, 10, 2023; (c) studies reporting the serological, cultural, and molecular techniques of IAs among newborns with and/or respiratory symptoms across the world; and (d) Reports related to the investigation of mentioned IAs in ≥31-day-old newborns. Research was excluded from this review if (a) samples were completely selected from infected newborns; (b) experimental research in animal models; and (c) review articles, clinical trials, case-reports congress abstracts, conference papers, meta-analysis, or systematic reviews and (d) articles in languages other than English as well as studies with misleading data/ difficult data interpretation.

Data extraction. The data were extracted from 44 selected studies (50 datasets), by two researchers separately and independently including the author’s name, location, publication year, study period, number of investigated patients, the number of IAs isolates, detection methods, sample type, and age range as well as isolated organism. Any issue related to the selection of studies was resolved by the first and corresponding authors.

Quality assessment. In the present review, we used the Joanna Briggs Institute (JBI) scoring system (9) to evaluate the quality of the included studies. This scoring-based checklist is designed for cross-sectional studies, which has 10 questions for each study and 4 yes/no/unclear/not applicable options for each answer. Therefore, each question can receive a maximum of one score and the numerical score of each study is between 0 and 10. In the quality assessment of this checklist, there are questions about the use of appropriate techniques and so on. We considered studies with 0 to 3 scores as poor quality and excluded them. On the other hand, studies with a score of 4-7 and 7-10, which were considered as intermediate and high quality respectively, were included for meta-analysis.

Data synthesis and statistical analysis. In this study, we performed all the steps of statistical analysis by comprehensive meta-analysis (V2.2, Bio stat) software. We used a random effect model (REM) to estimate the overall prevalence of the IAs. The prevalence results were displayed as a forest plot with 95% confidence interval (CI). The subgroup analysis was also performed based countries, time period of published studies (before and after 2010). The Egger’s test was applied to publication bias estimation and p-value<0.05 was representing statistically significant. As well, to calculating the studies heterogeneity, we used the both the Cochran's Q statistic and the I^2 statistic.

RESULTS

Study selection and studies characterization. After searching the above-mentioned databases, 2843 relevant studies were identified. Finally, 44 articles (50 datasets) were included based on the exclusion/ inclusion criteria in the meta-analysis (10-53). A summary of the research selection process and the reasons for exclusion is shown in flowchart of (Fig. 1).

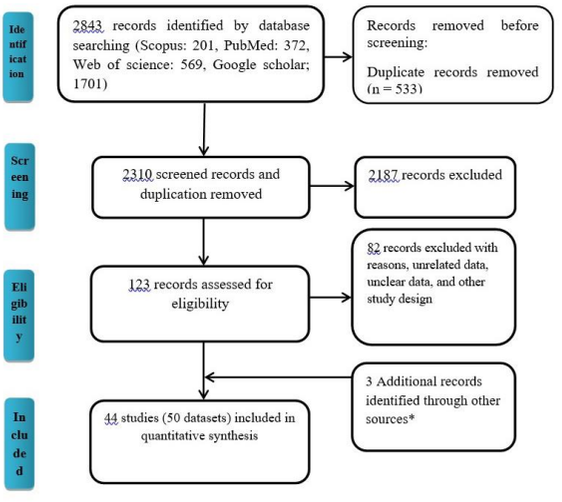

Fig. 1. Flow diagram of the literature search for studies included in meta-analysis. *Including manual search and library records.

Fourteen articles were performed in European region, 12 studies in America continent, 15 in Asia continent, 2 in Africa continent, and one study contained data with global geographic dispersion. Characteristics of the included 44 articles were showed in Table 1.

Pooled prevalence of infectious agents in the newborns. The total number of newborns included in this meta-analysis was 799339 based on the results of 44 articles. The pooled prevalence of IAs among newborns was 12.2% (95% CI: 6.40-22.0%) based on a random effects meta-analysis (Fig. 2). In sub-group analysis by countries, the highest prevalence of IAs was showed in Brazil (78.2%, 95% CI: 31.0-96.6%), whereas, in the UK (0.01%, 95% CI 0.01-0.01%) have a lowest prevalence (Table 2). Sub-group analysis based on the publication time period, the prevalence was 31.7% (95% CI: 5.6-78.5%) before 2010 and 9.0% (95% CI: 4.3- 17.7%) between 2011 and 2023.

Publication bias and heterogeneity assessment. The publication bias results were not significant by using Egger's regression test (P<0.053) (Fig. 3). Likewise, the I^2 statistics and Cochran's Q statistics results of revealed significant heterogeneity between the studies (Q =18368.185, P < 0.000, I^2 = 99.733%).

DISCUSSION

In the present meta-analysis, we assessed for the first time the global prevalence of infectious agents in life's first month of newborns with respiratory symptoms and those born to mothers with respiratory disorders, the overall prevalence of which was estimated to be 12.2% (95% CI: 6.40-22.0%). In order to meta-analyze the data, we included studies with laboratory reports of infectious agents, as well as some studies with retrospective data based on medical records. In the formation of infection, major factors such as the load, strain or species of the infectious agent, the state of the host's immune system, and the route of acquiring the infection are effective (54). As well, there are other risk factors for any pathogens or opportunists, which are bacterial infections, low level of personal and public hygiene, undeveloped and tropical areas (55). The most bacterial species reported from newborns in the studies were *Ureaplasma* species (*U. urealyticum* and *U. parvum*) and streptococci (group B), that the diagnostic method in these data was bacterial culture. Several scattered reports with case report designs of respiratory infections in newborns/infants are available, however, unfortunately, they do not have positive predictive value and analytical capabilities; therefore, the true prevalence rate is expected to be higher than the estimated values in the present study. Neonatal infections cause many worldwide morbidity and mortality, so the diagnosis of congenital or acquired infections early in life after birth, especially in the first month, is very critical (56, 57). Some newborns are born to mothers with respiratory disorders, so they can be premature babies and be born before the delivery time (58, 59). Prematurity of the baby or having an infection and/or respiratory disorder of the mother are risk factors for respiratory disorders in newborns (60). Considering the vulnerable level of immunity of newborns, acquiring an infection from the uterine-vaginal canal, from the hospital or home environment, or congenital infection can be considered as an opportunistic infection (61). Since the newborn's immune system

Table 1. General characterizations of the included studies.

First name	Pub year	Study period	Country	Method	Sample type	Total cases	Positive cases	Age (Range)	Infectious agent type
Twisselmann	2000	1992-1997	UK	NR	NR	63585	64	NR	Streptococ B
Vieira et al.	2001	1995-1996	Brazil	Cell culture, Indirect immunofluorescence assay (IFA)	Nasopharyngeal aspirates (NPA) and swabs (NPS)	14	13	NR	RSV
Gagneur et al.	2002	1997-1998	France	indirect immunofluorescence and Cell culture	Nasal specimens	64	7	<28 day	HCoV-229E, HCoV-OC43
Checon et al.	2002	1997-1998	Brazil	indirect immunofluorescence Histopathology	nasopharyngeal secretion	25	15	<30 day	RSV *Ureaplasma*
Benstein et al.	2003	NR	USA	Serology RT-	Tissue	11	7	<31 day	*urealyticum Streptococcus*
Hoffman et al.	2003	1993-2001	USA	PCR, IFA	Serum Nasopharyngeal	4428	29	<30 (18.1)	*pneumoniae* RSV
Fodha et al.	2004	2000-2002	Tunisia	ELISA	aspirates Cord Blood	268	62	day	*Bordetella pertussis (*anti-PT)
Gonik et al.	2005	NR	USA	ELISA	Cord Blood	101	45	35<	*Bordetella pertussis* (FHA)
Gonik et al.	2005	NR	USA	ELISA	Cord Blood	101	94	NR	*Bordetella pertussis (*PRN)
Gonik et al.	2005	NR	USA	Bacterial culture	Throat swabs	101	81	NR	*Ureaplasma urealyticum*
Abdulnabi and Al-Chalabi	2006	2003-2003	Iraq			80	36	NR	
Aydin et al.	2013	2010-2011	Turkiye	Multiplex RT-PCR	Nasopharyngeal aspirates	44	27	0-4 dav	RSV, Influenza A, Rhinovirus Parainfluenza-1,
Smit et al.	2013	2010-2011	Netherland	Real time PCR	Nasopharyngeal samples	334	34	NR	Human rhinovirus, Parainfluenza-3, RSV,
								<28 (1.3) day NR	*Streptococcus pneumoniae*, Adenovirus, human coronavirus, Influenza A, and bocavirus
Sobouti et al.	2014	2010-2011	Iran	PCR	Nasotracheal and pharyngeal specimens	165	33	<28 day	*Mycoplasma hominis* and *Ureaplasma urealyticum*
Mutlu et al.	2015	2010-2011	Turkiye	Respi-Strip kits	Nasopharyngeal swabs nasopharyngeal	41	15	<28 day	RSV
Lu et al.	2015	2010-2014	China	PCR, DFA	aspirates nasopharyngeal aspirates	1803	374	<28 day	RSV
Lu et al. 1	2015	2010-2014	China	PCR, DFA	Tracheal aspirate	1803	163	1 day	Influenza, Parainfluenza, Adenovirus
Abd-EL Rauf	2016	NR	Egypt	PCR	Tracheal aspirate	35	5	1 day	*U. parvum*
Abd-EL Rauf	2016	NR	Egypt	PCR	Nasopharyngeal aspirate	35	1	1 day	*U. urealyticum*
Rojas et al.	2017	NR	Spain	PCR	nasopharyngeal swab	128	33	1 day	*Pneumocystis jirovecii*
Vera et al.	2017	2015-2016	Colombia	Nested-PCR	NR	43	32		*Pneumocystis jirovecii*
Lee et al.	2017	2013-2015	Korea	Real time PCR		136	36	<28 day	RSV, Influenza, Parainfluenza virus, Rhinovirus, Corona virus
Maksic et al.	2018	2013-2014	Different countries	NR	NR	160	7	9 (8-16) day	RSV
Kumar et al.	2019	NR	India	PCR	endotracheal fluid, nasopharyngeal aspirates	60	14	Preterm NR	*Ureaplasma urealyticum, Ureaplasma parvum*
Liu et al.	2020	2020-2020	China	RT-PCR	Pharyngeal swabs	51	0	NR	SARS-CoV-2
Nie et al.	2020	2020-2020	China	Real time RT-PCR	throat swabs Cord	26	1	NR	SARS-CoV-2
Manti et al.	2020	2016-2019	Italy	IFA	Blood	16	8	NR	RSV SARS-
Xu et al.	2020	2020-2020	China	PCR	Pharyngeal swabs	23	0	NR	CoV-2
Farghali et al.	2020	2020-2020	USA	Real time RT-PCR	nasopharyngeal swab	79	15	NR	SARS-CoV-2
He et al.	2021	2020-2020	China	RT-PCR	feces, urine, blood, gastric juices, and throat swab	22	0	1 day	SARS-CoV-2
Lubis et al.	2021	2020-2020	Indonesia	Real time PCR	nasopharyngeal swab nasopharyngeal swab	43	5	1 day	SARS-CoV-2
Cardona-Perez et al.	2021	2020-2020	Mexico	RT-PCR	Serum	39	9	1 day	SARS-CoV-2
Pia et al.	2021	2020-2020	Denmark	Serology	nasopharyngeal swab	1206	17	1-2 day	SARS-CoV-2
Shlomai et al.	2021	2020-2020	Israel	Real time PCR	nasopharyngeal swab	55	0	1 day	SARS-CoV-2
Sanchez-luna et al.	2021	2020-2020	Spain	PCR	Nasal specimens	469	14	2 day	SARS-CoV-2
Solis-Garcia et al.	2022	2020-2020	Spain	PCR PCR	Nasal specimens	75	0	14 day	SARS-CoV-2
Solis-Garcia et al.	2022	2020-2020	Spain	Serology	Serum	54	1	NR	SARS-CoV-2
Vazquez-Alejo et al.	2022	2020-2020	Spain	Nested PCR	Nasopharyngeal aspirates	25	3	1 day	SARS-CoV-2
Szydłowicz et al.	2022	2018-2019	Poland	RT-PCR	nasopharyngeal swabs	56	8	NR	*Pneumocystis jirovecii*
Morioka et al.	2022	2020-2020	Japan	NR	NR	52	1	<28 day	SARS-CoV-2
Pan et al.	2022	2015-2020	China	NR	NR	13267	6251	<28 day	Respiratory infections (Pre COVID-19 cohort)
Pan et al. 1	2022	2015-2020	China	NR	NR	1201	556	< 30 day	Respiratory infections (COVID-19 cohort)
Wallace et al.	2022	2020-2020	USA	PCR	bronchial lavage samples Tracheal	701777	209	NR	SARS-CoV-2
Gonzalez-Fernandez	2023	2016-2019	Mexico	Bacterial culture	aspirate, nasopharyngeal swabs NR	1062	363	<28 day	Chlamydia trachomatis
Gobec et al.	2023	2009-2019	Slovenia	NR	NR nasopharyngeal	196	50	<2 day	*Ureaplasma* spp.
Eid et al.	2023	2020-2022	USA	PCR	swab nasopharyngeal	195	7	1 day	SARS-CoV-2
Jafari et al.	2023	2020-2022	Iran	PCR	swab nasopharyngeal	78	9	3 day	SARS-CoV-2
Lee et al.	2023	2020-2022	Korea	RT-PCR	swab	63	5	NR	SARS-CoV-2
Sengul et al.	2023	2021-2021	Turkiye	PCR		90	0	<10 day	SARS-CoV-2
Hudak et al.	2023	2020-2021	USA			7648	144		

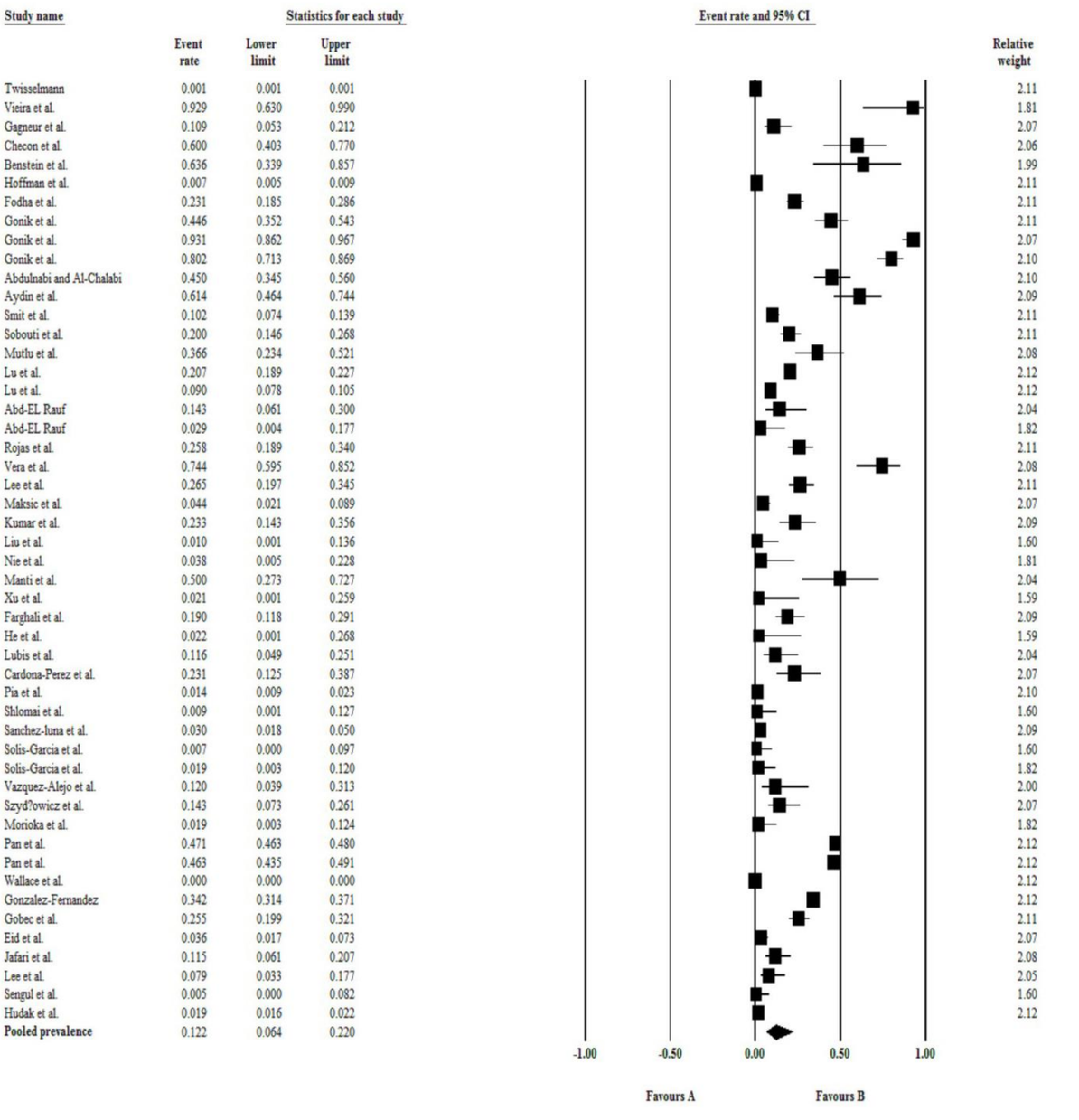

Fig. 2. Forest plot of the pooled prevalence for IAs in newborns

is not formed in the first days after birth, it depends solely on the maternal immunity, the primary defense barriers of the innate immune system such as the skin, the epithelium of respiratory tissues and local immune cells (62). Premature birth (premature and low birth weight) as well as defects in immune cell regulatory genes associated with incomplete maturation and/or function of the innate immune system increase the risk of infection (63). According to the findings of the present meta-analysis, the highest prevalence and reports were related to viral infections, especially RSV. It is interesting to note that the location of the organisms in the parts of the respiratory tract can be different, so that respiratory viruses are generally implanted in the part of the upper respiratory tract, which lead to symptoms such as cough, congestion and rhinorrhea (64). On the other hand, in lower respiratory tract infection, symptoms such as shortness of breath, respiratory distress and wheezing are more common, which may require ox-

Table 2. Pooled prevalence of IAs in newborns and subgroup analysis according to countries, and publication period.

Characteristics	Categories	No. of Data sets	Pooled prevalence (%) (95% CI)	Heterogeneity		
				Q value	P-value	I^2%
Overall	-	50	12.2 (6.40-22.0)	18368.185	0.000	99.733
Countries	Brazil	2	78.2 (31-96.6)	3.750	0.53	73.33
	China	8	15.9 (8-28.9)	1067.844	0.000	99.344
	Colombia	1	74.4 (59.5-85.2)	0.000	1.00	0.00
	Denmark	1	1.4 (0.9-2.3)	0.000	1.00	0.00
	Different countries	1	4.4 (2.1-8.9)	0.000	1.00	0.00
	Egypt	2	8.1 (1.7-31.2)	2.383	0.123	58.032
	France	1	10.9 (5.3-21.2)	0.000	1.00	0.00
	India	1	23.3 (14.3-35.6)	0.000	1.00	0.00
	Indonesia	1	11.6 (4.9-25.1)	0.000	1.00	0.00
	Iran	2	16.2 (9.4-26.5)	2.589	0.108	61.376
	Iraq	1	45 (34.5-56)	0.000	1.00	0.00
	Israel	1	0.09 (0.01-12.7)	0.000	1.00	0.00
	Italy	1	50 (27.3-72.7)	0.000	1.00	0.00
	Japan	1	1.9 (0.3-12.4)	0.000	1.00	0.00
	Korea (South)	2	15.8 (4.4-43.1)	8.011	0.005	87.518
	Mexico	2	31 (21.8-41.9)	2.026	0.155	50.638
	Netherland	1	10.2 (7.4-13.9)	0.000	1.00	0.00
	Poland	1	14.3 (7.3-26.1)	0.000	1.00	0.00
	Slovenia	1	25.5 (19.9-32.1)	0.000	1.00	0.00
	Spain	5	5.4 (1.2-20.4)	59.890	0.000	93.321
	Tunisia	1	23.1 (18.5-28.6)	0.000	1.00	0.00
	Turkiye	3	26.9 (7-64.2)	18.111	0.000	88.957
	UK	1	0.01 (0.01-0.01)	0.000	1.00	0.00
	USA	9	12.4 (1.3-60.4)	3981.510	0.000	99.799
Publication period	2000-2010	11	31.7 (5.6-78.5)	2231.626	0.000	99.552
	2011-2023	39	9 (4.3-17.7)	15322.110	0.000	99.752

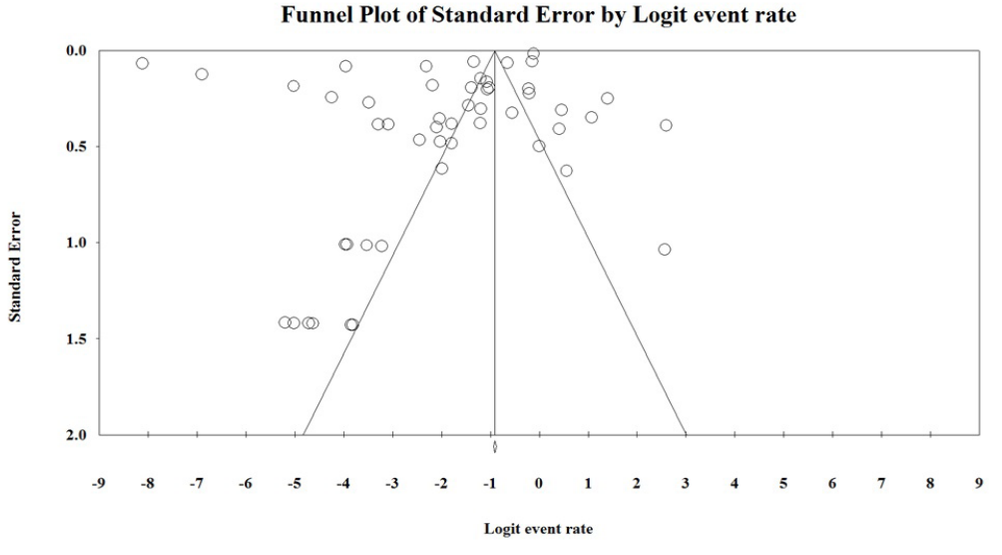

Fig. 3. Funnel plot for publication bias assessment

ygenation and ventilation for control and treatment purposes (65). In the case of viral infections, they can occasionally cause systemic infection in the baby's body and even lead to secondary bacterial infection, which clearly has different symptoms of systemic infection, including tachypnea, apnea, body temperature instability, and feeding disorders (66). We should not forget that respiratory infections of viral origin, such as some enteroviruses, adenoviruses, and some newly emerging viruses, can cause clinical manifestations outside the respiratory system, such as hepatitis, meningoencephalitis, perimyocarditis, and gastrointestinal infections it has been reported many times that it can probably be caused by the spread of the virus in other organs; Therefore, in the diagnosis of neonatal infections, the entire clinical picture of the patients is significant (67).

Although in the majority of studies, the detection method was molecular based, however, in a number of studies, some techniques with lower sensitivity and specificity (e.g. ELISA test) were also used, and the difference in the accuracy of the tests could overshadow the results; so that it seems that the estimated prevalence rate is lower than the true prevalence values.

As mentioned, the strain or types of the infectious agent, especially viruses, are critical in pathogenesis, in the case of parainfluenza, types 1 and 3 have been the most isolated types of respiratory infections (68). Also, a very important variable in the prevalence of viral infections is their seasonal prevalence, except for adenoviruses, which are possible to be transmitted throughout the year; most respiratory viruses are more prevalent in winter seasons in areas with moderate climate (69). Lately, the COVID-19 pandemic focused attention on the diagnosis of SARS-CoV-2 in newborns and changed the pattern of RIs in its favor, so that the prevalence and reporting of other RIs diminished (70). The lack of a suitable vaccine to prevent viral RIs, as well as the antigenic switch of viral strains, has made the prevention of these infections a challenge. From a molecular point of view, viruses can affect the host's biological systems by changing the host's cellular and molecular factors such as non-coding RNAs (e.g. microRNAs, lncRNAs, etc.) (71). In this regard, it seems that human rhinovirus can induce or exacerbate asthma in infected hosts by changing the expression and/or production of inflammatory and pro-inflammatory mediators, which is a point worth considering (72).

Unlike parasites, there have been reports of *Pneumocystis jirovecii (P. jirovecii)* fungal infection, also known as *Pneumocystis carinii*. Due to the pathogenicity of *P. jirovecii* in people with insufficient immunity, the infection of newborns/infants with a similar condition can be considered hazardous (26). There is a hypothesis that this fungal agent has a maternal transmission, and studies have investigated the prevalence and probability of mother-to-infant transmission in both pairs of mothers and newborns (73).

The current study has faced limitations that include 1) lack of determination and reporting of some species or types of infectious agents, 2) lack of using a diagnostic technique with appropriate sensitivity and specificity in some reports, 3) unavailability of exact age of some studies, 4) lack of information on the severity of respiratory symptoms of newborns, which can depend on the strain/type; 5) absence of epidemiological investigations with the season of outbreak of infections (viral), which season can overshadow the prevalence rate; 6) the existence of some studies in languages other than English and 7) clinical interventions in many studies, such as vaccination programs or drug testing trials, which are an effective factor in the incidence and prevalence of infectious agents.

CONCLUSION

According to the findings based on our analysis, the prevalence of infectious (respiratory) agents in infants with or without respiratory symptoms has been significant. Our findings emphasize the importance of early identification and diagnosis of infections in infants as well as preventive measures and reinforce the need to use more accurate techniques with details of infectious agents. As suggestions for future studies, it is suggested to conduct studies with a large and matched sample size, it is better to use techniques with high sensitivity and specificity such as molecular methods. In future studies, the age of newborns should be precisely categorized and mentioned. It is better to determine the species of infectious agents so that the interpretations of the results are more accurate.

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