RSV bronchiolitis in 2018: A descriptive study of children admitted to two Johannesburg tertiary hospitals

T S Cleak,[1] FCPaed (SA), DCH (SA), DipHIVMan (SA); **D E Ballot**,[1] FCPaed (SA), PhD;
N M Moshesh,[2] FCPaed (SA), Cert Crit Care (Paeds); **L Chirwa**,[2] FC Paed (SA), Cert Neonatology;
T Thomas,[3] FCPath Micro, DTM&H, DipHIVMan (SA); MMed (Micro);
D A White,[1] FC Paed (SA), MMed (Paed), Dip Allergy (SA), Cert Pulmonology (SA) Paed

[1] *Charlotte Maxeke Johannesburg Academic Hospital, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Nelson Mandela Children's Hospital, Johannesburg, South Africa*
[3] *Infection Control Services Laboratory, Department of Microbiology, National Health Laboratory Service, Johannesburg, South Africa*

Corresponding author: *T S Cleak (tannahcleak@gmail.com)*

Background. Respiratory syncytial virus (RSV) is the most common cause of severe bronchiolitis in children worldwide.
Objectives. To describe clinical characteristics and outcomes of children hospitalised with bronchiolitis and to compare those with RSV bronchiolitis with children with other viral causes of bronchiolitis.
Methods. A retrospective study of children admitted with virally screened bronchiolitis to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Nelson Mandela Children's Hospital (NMCH) from 1 February to 31 August 2018 was conducted, where RSV-positive and -negative children were compared. These children were identified by the National Health Laboratory Service as having undergone respiratory viral multiplex molecular assay analysis and hospital charts were retrospectively reviewed.
Results. A total of 131 children admitted with bronchiolitis from CMJAH and NMCH were compared in this study, 58 from CMJAH and 73 from NMCH. In the sample group, 65 (49.6%) children had RSV in comparison with 66 (50.4%) children without RSV. Children with RSV comprised 55 (42%) children with RSV only and 10 (7.6%) children with RSV in combination with another respiratory virus. Rhinovirus was the second most common virus detected in this cohort of children (n=17, 12.9%) followed by adenovirus (n=12, 9.2%) and coronavirus (n=9, 6.9%). A statistically significant risk factor noted in children requiring hospitalisation for RSV bronchiolitis was age less than six months (p<0.001).
Conclusions. Bronchiolitis is a common disease in children. Respiratory syncytial virus is the most common cause of severe bronchiolitis in hospitalised infants less than six months of age.

S Afr J Child Health 2023;17(3):e1984. https://doi.org/10.7196/SAJCH.2023.v17i3.1984

Bronchiolitis is a lower respiratory tract infection caused by many viruses, primarily affecting children younger than two years.[1,2] In South Africa, the overall prevalence of respiratory viruses in children with a lower respiratory tract infection and under the age of five was 78%.[3] Respiratory viruses causing bronchiolitis include rhinovirus, respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, influenza virus, human metapneumovirus, bocavirus, coronavirus and measles virus.[1,2] RSV is the most common cause of severe bronchiolitis[1,2,4,5] and accounts for 40 - 90% of hospitalisations for children admitted with bronchiolitis.[4,5] The increasing burden of RSV, particularly in infants, has been well documented worldwide.[4,5]

Risk factors include infancy, male gender and underlying medical conditions, including prematurity, bronchopulmonary dysplasia and congenital lung disease of infancy, congenital lung malformations, haemodynamically significant congenital heart defects, neuromuscular disease, immune compromise, and lack of breastfeeding. [2,6,7] Environmental risk factors attributing to severe illness include tobacco smoke exposure, overcrowding and day-care attendance.[2,7] It is possible for children to suffer from severe re-infections with RSV despite having humoral immunity from previous infections.[8] Seasonality depends on the geographical location in South Africa. In the temperate areas it is after the rainy season, approximately February to June, and in the coastal areas it follows the rainy season.

Infection with RSV and other respiratory viruses typically begins with an upper respiratory prodrome consisting of coryzal symptoms and low-grade fever.[6,8,9] If these respiratory viruses spread to the lower airways, bronchiolitis may develop as evidenced by a pattern of wheezing and hyperinflation.[6] Chest radiography is not routinely performed for bronchiolitis, but can be requested in cases with suspected complications.[10] There may be a role for routine viral screening for surveillance and understanding the possible contributing role of co-infection with multiple viruses.[11,12] Management for all cases of bronchiolitis, mild to severe, remains supportive. [13,14] Treatment goals include managing hypoxia, pyrexia and optimising nutrition. [13,14]

The present study aimed to determine and compare clinical characteristics, risk factors, co-infections and outcomes for children admitted with RSV-positive and RSV-negative bronchiolitis at two state tertiary hospital centres in Johannesburg.

Methods

This study was a retrospective, descriptive analysis of children younger than two years admitted to Charlotte Maxeke Johannesburg

Academic Hospital (CMJAH) and Nelson Mandela Children's Hospital (NMCH) with virally screened bronchiolitis from 1 February 2018 to 31 August 2018. Children with RSV-positive bronchiolitis were compared with those children with RSV-negative bronchiolitis.

Study sites

CMJAH is a tertiary hospital incorporated into the academic circuit of the health science programme at the University of the Witwatersrand. The 220-bed paediatric service caters for all paediatric medical and surgical subspecialties. There are 14 beds available in the mixed paediatric and neonatal intensive care. CMJAH serves a large population including many referring clinics and hospitals. These include Bertha Gxowa Hospital, South Rand Hospital, Edenvale Hospital, Tambo Memorial Hospital, Pholosong Hospital and Far East Rand Hospital.

NMCH, a new tertiary facility in close proximity to CMJAH, opened three years ago. The hospital has both a paediatric and neonatal ICU, admitting up to 16 patients each. Paediatric cardiology and renal patients also receive care at NMCH.

Data collection

Nasopharyngeal swab or tracheal aspirate specimens were submitted to the National Health Laboratory Service (NHLS) for viral multiplex molecular assay analysis for patients admitted with respiratory tract infections. Multiplex molecular assays detect viral nucleic acids.[15] Respiratory viral specimens from CMJAH and NMCH were sent to NHLS and Lancet Laboratories, respectively. Multiplex polymerase chain reaction (PCR)-based respiratory viral panels performed at NHLS tested for influenza virus, adenovirus and RSV, while respiratory panels at Lancet tested for adenovirus, bocavirus, coronavirus, enterovirus, influenza virus, human metapneumovirus, mycoplasma pneumonia, parainfluenza, parechovirus, RSV and rhinovirus. The NHLS infection control specialists supplied lists of individuals who had undergone viral testing for bronchiolitis during the study period. These lists were reviewed and patients older than two years and from other hospitals were excluded. Hospital records of those children who were admitted with an initial diagnosis of bronchiolitis and met the specified study criteria, were reviewed. Mild, moderate and severe bronchiolitis was determined according to the modified TAL score which takes into account the patient's respiratory rate, use of accessory muscles, presence of wheeze or crackles and saturation levels on room air.[16] Children who were in moderate or severe respiratory distress and hypoxic on room air were admitted. Children from both CMJAH and NMCH's paediatric general ward and intensive care units were included in this study. Management was supportive, and oxygen therapy modalities were escalated as necessary to maintain patients' saturation above 90%.

Clinical, demographic, serological and radiological data were captured according to a pre-designed data collection sheet. The reference ranges provided by the NHLS were used to categorise the children's results.[17] Survivors were those children who were discharged home or transferred from CMJAH or NMCH back to their base hospitals.

Statistical analysis

An MS Excel (Microsoft Corp., USA) spreadsheet was used to enter the data, which were then imported into statistical software package SPSS version 25 (IBM Corp., USA). Frequencies and percentages were used to describe categorical variables. Means and standard deviations were used to describe normally distributed, continuous variables. The chi-square test and *t*-test were used to compare categorical and continuous variables, respectively. A *p*-value <0.05 was considered significant.

Ethics

The Human Research Ethics Committee of the University of the Witwatersrand granted approval for the study (ref. no. M190505).

Results

During the study period, 152 children had viral specimens submitted for testing. A total of 21 participants were excluded from further analysis for the following reasons: one incorrect patient file, five missing records and 15 nosocomial diagnoses of bronchiolitis. The total number of children who were admitted with bronchiolitis or who underwent swabbing is not known. The remaining cohort included 131 children, 58 from CMJAH and 73 from NMCH.

The most common virus isolated in children admitted with bronchiolitis to CMJAH and NMCH was RSV (*n*=65, 50%). Rhinovirus was the second most common virus detected in children (*n*=17, 13%) followed by adenovirus (*n*= 12, 9%) and coronavirus (*n*=9, 7%). There were 17 (13%) children who cultured more than one respiratory virus. Table 1 demonstrates the children's viral multiplex-PCR results.

The majority of children in this study were aged six months and younger (*n*=74, 57%), with more than half of these children having RSV-positive bronchiolitis (*n*=47/75, 63%). The remaining children consisted of 45 (34%) between the ages of 7 - 11 months and 12 (9%) older than one year. Only 42 (32%) children were born prematurely, i.e. less than 37 weeks' gestation, with the majority of these children

Table 1. Viral multiplex PCR (*N*=131) results of children admitted with bronchiolitis

Virus	*n* (%)
RSV total	65 (50)
RSV only	55 (42)
RSV and other viruses	10 (8)
RSV and rhinovirus	3 (2)
RSV and adenovirus	2 (2)
RSV and bocavirus	1 (1)
RSV and coronavirus	1 (1)
RSV and influenza A virus	1 (1)
RSV, bocavirus and coronavirus	1 (1)
RSV, coronavirus and parainfluenza	1 (1)
Total of other viruses	66 (50)
Rhinovirus	13 (10)
Adenovirus	5 (4)
Influenza A virus	5 (4)
Coronavirus	4 (3)
Human metapneumovirus	3 (2)
Parainfluenza	2 (2)
Enterovirus	2 (2)
Influenza B virus	1 (1)
Combination of other viruses	6 (5)
Adenovirus and parainfluenza	3 (2)
Adenovirus and coronavirus	1 (1)
Adenovirus and influenza B virus	1 (1)
Rhinovirus and coronavirus	1 (1)
No virus detected	25 (19)

RSV = respiratory syncytial virus.

(*n*=24/42, 57%) having RSV-positive bronchiolitis. However, prematurity was not a statistically significant risk factor for children having RSV-positive bronchiolitis compared with children with non-RSV bronchiolitis. Children in this study were predominantly not exposed to HIV at birth (*n*=81, 62%). Only three children with HIV exposure were confirmed to be HIV positive with further testing. HIV did not demonstrate any statistical difference in children presenting with RSV-positive bronchiolitis. There were not enough data for the following risk factors: feeding choice, other immunodeficiency states, siblings attending crèche or tobacco smoke exposure to compare and comment on in the context of this study. Table 2 compares other risk factors between RSV-positive and -negative bronchiolitis participants. The only statistically significant risk factor for RSV bronchiolitis was age less than six months (*p*-value <0.001).

There was no statistically significant difference between both laboratory and radiological investigations performed on RSV-positive and RSV-negative children with bronchiolitis. A multivariable regression analysis showed that none of the above listed risk factors was found to be dependently associated with RSV, as evidenced by a *p*-value >0.05 for each variable. The majority of initial chest radiographs for children with RSV-positive bronchiolitis were hyperinflated with infiltrates (*n*=33/65, 51%). Children with RSV-negative bronchiolitis generally had infiltrates only on their chest radiographs (*n*=38/66, 58%). There were eight positive admission blood cultures for children with RSV and seven for children without RSV bronchiolitis. No clinically significant organisms were cultured for children with RSV bronchiolitis. While two children without RSV grew *Staphylococcus aureus* and one *Escherichia coli*, the remaining cultures were clinically insignificant.

Complications, outcomes, oxygen therapy and length of admission are summarised in Table 3. A total of 103 (79%) children required admission to CMJAH's and NMCH's ICU facilities for invasive methods of ventilation during the study, 54 children with RSV and 49 without RSV. The remaining 28 (21%) children were cared for in the general wards. More than half of children from this study were investigated for nosocomial sepsis, 49 with RSV bronchiolitis and 43 without RSV. There were 11 children with RSV and 15 without RSV who had evidence of nosocomial sepsis on blood cultures. Children with RSV cultured the following organisms: one *Acinetobacter baumannii*, one *Candida albicans*, one *Escherichia coli*, two *Klebsiella pneumoniae*, two *Staphylococcus aureus* and four clinically insignificant organisms (coagulase-negative *Staphylococcus)*. Children without RSV cultured the following organisms: one *Acinetobacter baumannii*, one *Candida albicans*, one *Escherichia coli*, one methicillin-resistant *Staphylococcus aureus*, one *Pseudomonas aeruginosa*, two *Staphylococcus aureus* and eight clinically insignificant organisms.

In the present study, children stayed at CMJAH and NMCH for an average of 14.5 days (*s*=10.3 days), and admissions to ICU averaged 10.1 days (*s*=8.1 days). Children required oxygen therapy for approximately 13.4 days (*s*=9.7days).

Children with RSV bronchiolitis were predominantly admitted in March and April of 2018, with some later admissions in July and August (Supplementary Fig. 1 https://www.samedical.org/file/2060). Rhinovirus was the second most common virus found from April to August.

Discussion

This present study, conducted at two large academic referral centres in Johannesburg, South Africa, demonstrated that RSV was the most common virus detected in children hospitalised with moderate and severe bronchiolitis in the 2018 season (*n*=65,

Table 2. Comparison of risk factors for children with and without RSV infection

Risk factor	RSV-positive *N* 65, *n* (%)	RSV-negative *N* 66, *n* (%)	*p*-value
HIV unexposed	36 (55)	45 (68)	0.09
HIV exposed	29 (45)	21 (32)	
HIV PCR positive	2 (3)	1 (2)	0.49
HIV ELISA/PCR negative	63 (97)	65 (99)	
Premature	24 (37)	18 (27)	0.16
Congenital heart disease*	9 (14)	18 (27)	0.05
Chronic lung disease†	26 (40)	22 (33)	0.27
<6 months old	47 (72)	27 (41)	<0.001

RSV = respiratory syncytial virus; PCR = polymerase chain reaction.
*Congenital heart disease with increased blood flow, consisting of: ventricular septal defects, atrial septal defects, atrioventricular septal defects and patent ductus arteriosus.
†Chronic lung disease was predominantly secondary to bronchopulmonary dysplasia (*n*=21/48), when specified in the respective children's hospital records. However, the remaining children's records did not specify the underlying cause for their chronic lung disease.

Table 3. Comparison of complications, outcomes and oxygen therapy for children with and without RSV infection

Complications and outcomes		RSV-positive *n/N* (%)	RSV-negative *n/N* (%)	*p*-value
Nosocomial sepsis		49/65 (75)	43/66 (65)	0.18
Apnoea		35/65 (53)	30/66 (46)	0.38
Cardiopulmonary resuscitation		9/65 (14)	14/66 (21)	0.35
Hypotension requiring inotropes		9/65 (14)	18/66 (27)	0.8
Seizures		5/65 (8)	2/66 (3)	0.27
Pulmonary hypertension		3/65 (5)	7/66 (11)	0.61
Myocarditis		4/65 (6)	5/66 (8)	0.78
Ventilation-acquired pneumonia		13/65 (20)	11/66 (17)	0.78
Outcomes	Death	7/65 (5)	10/66 (8)	0.64
	Discharge	58/65 (44)	56/66 (42)	
Days on oxygen	NPO_2	216/883 (25)	264/844 (31)	0.67
	$HFNO_2$	106/883 (12)	138/844 (16)	
	CPAP	16/883 (2)	4/844 (1)	
	CMV	429/883 (49)	319/844 (38)	
	HFOV	116/883 (13)	86/844 (10)	
	ECMO	0/883 (0)	33/844 (4)	
Length of admission (days)		945 (52)	873 (48)	0.27

RSV = respiratory syncytial virus; CPAP = continuous positive airway pressure; CMV = cytomegalovirus; HFOV = high-frequency oscillatory ventilation; ECMO = extracorporeal membrane oxygenation.

49.6%). Seventeen children had more than one virus identified on their respective viral swabs but the implications, i.e. determining if one specifically or the combination of all the viruses determined the severity of illness, duration of illness and subsequent outcomes for those respective children, cannot be determined in the context of this study. The next most common viruses identified in this study were adenovirus (n=12, 9.2%) and coronavirus (n=9, 6.9%).

Children with RSV presented mostly in March and April, with fewer RSV cases from May to August of 2018 (Fig. 2). This is in keeping with the seasonality described for RSV in Gauteng, with a peak around autumn.[1,2]

A number of well-described risk factors have been associated with increased frequency and severity of RSV bronchiolitis.[5] In the present study, infants under six months of age were more likely to be admitted with RSV-positive bronchiolitis compared with other viruses (p<0.001). More children with RSV bronchiolitis were premature and had chronic lung disease in comparison with RSV-negative children, but these factors were not statistically significant in this study, which was unexpected when reviewing the data in comparison with other local and international studies. HIV-infected children are more likely to have pneumonia than bronchiolitis, and HIV has been postulated to possibly be protective against RSV.[2] This was not the case in our study, as more participants with RSV bronchiolitis were HIV exposed or positive, although this did not reach statistical significance. There were not enough data available to comment on the impact of environmental risk factors on the children from this study.

Initial investigations, including haematological and radiological studies, yielded no statistical differences between children who were RSV positive or negative. This observation is in keeping with current literature that bronchiolitis should be diagnosed clinically, assessing the disease severity from history and examination findings.[9] There may be some value in performing routine viral screening for all children presenting with bronchiolitis, as it would contribute to epidemiological data as well as to cohort children with specific viruses. However, routine viral testing may not be viable in resource-limited settings, especially as treatment for children with bronchiolitis remains supportive regardless of the infecting organism. However, in light of the Covid-19 pandemic, other treatment modalities have been tried and tested in the management of children admitted with coronavirus, which supports routine viral screening for children admitted with any presentation of respiratory illness.

The majority of children in this study required admission to CMJAH's and NMCH's intensive care units (n=103, 78.6%). More than half of these children (n=54/103, 52.4%) had RSV bronchiolitis. This finding is comparable with other studies that have been conducted globally with regard to the large number of children needing hospitalisation for moderate or severe bronchiolitis having confirmed RSV.[4]

More children from the RSV-positive group were investigated for nosocomial sepsis in comparison with the RSV-negative group of children. This may be due to the fact that children with RSV were admitted for longer than children who did not have RSV, but this was not found to be statistically significant. Almost all the children admitted with bronchiolitis were discharged (n=114, 87.0%) home or back to their base hospital, despite the large number of children needing ICU admission and care. A total of 17 children died, 10 (7.6%) from the RSV-negative group of children and seven (5.3%) from the RSV-positive group. It is difficult to compare this finding to international mortality estimations as the total numbers of cases of bronchiolitis and all possible causative organisms were not known in this study.

Conclusion

In keeping with the international literature, RSV was the most common virus isolated in this cohort of hospitalised children (65/131, 49.6%) with bronchiolitis.[1,2,4,5] The majority of children were under six months of age (75/131, 57.3%) and infants less than six months of age were more likely to have RSV-confirmed bronchiolitis than those without (p-value <0.001). RSV cases peaked around autumn in 2018, in keeping with the described local seasonality of RSV.[1] Despite requiring hospitalisation, 114 of the 131 children in this study survived to discharge.

Study strengths and limitations

This study adds to the South African pool of data, specific to Johannesburg, available on RSV. However, only one RSV season was analysed, and true prevalence of RSV bronchiolitis cannot be determined from this analysis. It is also possible that a selection bias occurred as it was not standard practice to routinely swab children with bronchiolitis, therefore most likely only the sickest children were swabbed. Not all data were available from participants' files, which limited accurate comparisons between children with and without RSV.

Declaration. This article was submitted in partial fulfilment of the degree of Master of Medicine in the discipline of paediatrics at the University of the Witwatersrand.

Acknowledgements. None.

Author contributions. TSC: protocol, data collection, write-up; TT: supplied NHLS raw data, review and advice; NMM and LC: review and advice; DEB and DAW: oversight, advice and editing.

Funding. None received.

Conflicts of interest. None.

1. White DA, Madhi SA, Jeena P, et al. Acute viral bronchiolitis in South Africa: Viral aetiology and clinical epidemiology. S Afr Med J 2016;106(5):443-445. https://doi.org/10.7196/SAMJ.2016.v106i5.10444
2. Dearden CX, Jeevarathnum AC, Havinga J, Green RJ. The epidemiology of respiratory syncytial virus: A retrospective review from Steve Biko Academic Hospital 2013-2016. AJTCCM 2018;24(1):30-35. https://doi.org/10.7196/ajtccm.2017.v24i1.163
3. Cohen C, Walaza S, Moyes J, et al. Epidemiology of viral-associated acute lower respiratory tract infection among children <5 years of age in high HIV prevalence setting, South Africa, 2009-2012. Pediatr Infect Dis 2015;34(1):66-72. https://doi.org/10.1097/inf.0000000000000478
4. Walsh EE, Englund JA. Respiratory syncytial virus. In: Benett JE, Blaser MJ, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Ninth revised ed. Philadelphia: Elsevier – Health Sciences Division; 2019: 2093 -2103. https://doi.org/10.1016%2FB978-1-4557-4801-3.00160-0
5. Giovanni MD. RSV infections: State of the art. Cleve Clin J Med 2015;82(1):s13-s18. https://doi.org/10.3949/ccjm.82.s1.03
6. Meissner HC. Viral bronchiolitis in children. N Engl J Med 2016;374(1):62-72. https://doi.org/10.1056/nejmra1413456
7. Chávez-Bueno S, Mejías A, Jafri HS, Ramilo O. Respiratory syncytial virus: Old and new approaches. Pediatr Ann 2005;34(1):62-68. https://doi.org/10.3928/0090-4481-20050101-14
8. White DA, Zar HJ, Mahdi SA, et al. Acute viral bronchiolitis in South Africa: Diagnostic flow. S Afr Med J 2016;106(4):328-329. https://doi.org/10.7196/SAMJ.2016.v106i4.10704
9. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: The diagnosis, management and prevention of bronchiolitis. Pediatr Ann 2014;134:e1474-e1502. https://doi.org/10.1542/peds.2014-2742
10. Hervás D, Reina J, Yañez A, del Valle JM, Figuerola J, Hervás JA. Epidemiology of hospitalisation for acute bronchiolitis in children: Differences between RSV and non-RSV bronchiolitis. Eur J Clin Microbiol Infect Dis 2012;31(8):1975-1981. https://doi.org/10.1007/s10096-011-1529-y
11. Heikkinen T, Marttila J, Salmi AA, Russkanen O. Nasal swab versus nasopharyngeal aspirate for isolation of respiratory viruses. J Clin Microbiol 2002;40(11): 4337-4339. https://doi.org/10.1128/jcm.40.11.4337-4339.2002

12. Pretorius MA, Mahdi SA, Cohen C, Naidoo D, Groome M, Moyes J. Respiratory viral coinfections identified by 10-plex real-time reverse-transcription polymerase chain reaction assay in patients hospitalised with severe respiratory illness – South Africa, 2009-2010. J Infect Dis 2012;206(1):s159-s169. https://doi.org/10.1093/infdis/jis538
13. Zar HJ, Mahdi SA, White DA, et al. Acute viral bronchiolitis in South Africa: Strategies for management and prevention. S Afr Med J 2016;106(4):330-332. https://doi.org/10.7196/SAMJ.2016.v106i4.10437
14. Morrow BM, Feldman C, Green RJ. Acute viral bronchiolitis in South Africa: Intensive care management for severe disease. S Afr Med J 2016;106(5):446-448. https://doi.org/10.7196%2FSAMJ.2016.v106i5.10436
15. Brennan-Krohn T. Making sense of respiratory viral panel results. ASM, 2020. https://asm.org/Articles/2020/March/Making-Sense-of-Respiratory-Viral-Panel-Results (accessed 22 July 2021). https://asm.org/Articles/2020/March/Making-Sense-of-Respiratory-Viral-Panel-Results
16. Golan-Tripto I, Goldbart A, Akel K, et al. Modified Tal score: Validated score for prediction of bronchiolitis severity. Pediatr Pulmonol 2018;53(6):796-801. https://doi.org/ 10.1002/ppul.24007
17. Schmidt BM, Tameris M, Geldenhuys H, et al. Comparison of haematology and biochemistry parameters in healthy South African infants with laboratory reference intervals. TM & IH 2018; 23(1):63-68. https://doi.org/10.1111/tmi.13009

Accepted 8 May 2023.