Serum $\beta_2$-microglobulin may be a viral biomarker by analyzing children with upper respiratory tract infections and exanthem subitum: a retrospective study

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ABSTRACT

**Background.** Due to the lack of effective and feasible viral biomarkers to distinguish viral infection from bacterial infection, children often receive unnecessary antibiotic treatment. To identify serum $\beta_2$-microglobulin that distinguishes bacterial upper respiratory tract infection from viral upper respiratory tract infection and exanthem subitum in children.

**Methods.** This retrospective study was conducted from January 1, 2019 to September 30, 2020 in Yancheng Third People’s Hospital. Children with upper respiratory tract infection and exanthem subitum were recruited. The concentration of serum $\beta_2$-microglobulin in the viral and bacterial infection groups were statistically analyzed.

**Results.** A total of 291 children included 36 with bacterial upper respiratory tract infection (median age, 13 months; 44.4% female), 197 with viral upper respiratory tract infection (median age, 12 months; 43.7% female) and 58 with exanthem subitum (median age, 13 months; 37.9% female). When the concentration of $\beta_2$-microglobulin was 2.4mg/L, the sensitivity to distinguish viral from bacterial upper respiratory tract infection was 81.2% (95% CI [75.1–86.4%]), and the specificity was 80.6% (95% CI [64.0–91.8%]). When the cutoff was 2.91 mg/L, the sensitivity of $\beta_2$-microglobulin to distinguish exanthem subitum from bacterial upper respiratory tract infection was 94.8% (95% CI [85.6–98.9%]), and the specificity was 100% (95% CI [90.3–100%]).

**Conclusions.** Serum $\beta_2$-microglobulin may be a significant biological indicator in children with upper respiratory tract infection and exanthem subitum.

INTRODUCTION

Upper respiratory tract infection (URTI) is a common disease in children. Children with URTI often go to the outpatient or emergency department because of fever. In addition to fever, the clinical manifestations of children with URTI include runny nose, sneezing, hoarseness, pharyngeal congestion, mild dry cough and swelling of tonsil (Weintraub, 2015). The early manifestation of exanthem subitum is similar to acute URTI. The early main
symptoms of exanthem subitum is persistent high fever, and the clinical symptoms of runny nose, pharyngeal congestion and tonsil swelling will also appear (Robert Kliegman, 2019; Stone, Micali & Schwartz, 2014). Exanthem subitum usually depends on the characteristics of rash appearance after the disappearance of fever for retrospective diagnosis (Stone, Micali & Schwartz, 2014). The age of children with exanthem subitum is mostly between 6 months and 24 months (Hattori et al., 2019). It is challenging to distinguish acute URTI from early stage exanthem subitum according to clinical manifestations and symptoms.

Most of the pathogens of acute URTI are viruses (Wei et al., 2017). There are also a small number of bacteria (Bellussi et al., 2019). Common virus infection (adenovirus, Parainfluenza virus and respiratory syncytial virus) only need symptomatic treatment (Tang et al., 2019). Influenza virus infection should be treated with anti influenza drugs. Antibiotics are required for bacterial infections. However, there is an obvious overuse of antibiotics in children with viral URTI (Cheng et al., 2019).

Exanthem subitum caused by human herpesviruses 6 and 7 usually recovers well and only needs symptomatic treatment (Stone, Micali & Schwartz, 2014). Exanthem subitum is often accompanied by neutropenia and leucopenia (Arnež et al., 2016). Sepsis can also be characterized by fever and neutropenia (Das, Trehan & Bansal, 2018; Dien Bard & Mongkolrattanothai, 2019). Therefore, persistent high fever, neutropenia and leucopenia in the early stage of exanthem subitum can easily lead to misdiagnosis, such as URTI and sepsis. And then, there may be antibiotic abuse.

A study found that β2-microglobulin (β2-MG) expression was closely related to cytotoxic T cells in a mouse model (Zijlstra et al., 1990). Interestingly, the activation of cytotoxic T cells participate in the immune response to viral infection (Baugh, Tzannou & Leen, 2018; David et al., 2019; Langellotti et al., 2020). A previous study found that β2-MG was significantly increased in viral lower respiratory tract infection, and it may distinguish viral infection from bacterial infection (Cai et al., 2020). This study analyzed the distribution characteristics of β2-MG in children with exanthem subitum and acute URTI. We explored the theoretical basis of identification of viral infection by β2-MG.

**METHODS**

**Study population**

The subjects were children who visited to our hospital between January 1, 2019 and September 30, 2020. We collect information by browsing the electronic medical record. This study conducted a retrospective study on acute URTI and exanthem subitum.

Inclusion criteria: (1) Acute URTI and exanthem subitum were diagnosed by experienced specialists. (2) The age of children with exanthem subitum is mainly between 6 months and 24 months. We collected children between 6 months and 24 months. (3) Each case was infected with only one pathogen. (4) Serum β2-MG detection had been completed in the acute stage of acute URTI and in the febrile period of exanthem subitum.

Exclusion criteria: (1) Combined with other infectious diseases. (2) Children have immune deficiency and hereditary diseases. (3) There was kidney disease. Because β2-MG is affected by renal filtration rate. (4) The children had used immunosuppressive drugs in the last two weeks.
The project was approved by the ethics committee of the Yancheng Third People’s Hospital (Approval Number: 2019100). Informed consent was waived by the ethics committee of the Yancheng Third People’s Hospital because the study was considered to pose the least risk to participants.

Identification of pathogen
All cases were examined for viral and bacterial pathogens. Common viral pathogens were detected, including influenza A virus, influenza B virus, adenovirus, respiratory syncytial virus, parainfluenza virus and human herpesviruses 6. Viral infection: (1) The identification of respiratory virus is through antigen detection or PCR nucleic acid detection of nasopharynx swab samples. (2) The infection of human herpesviruses 6 was confirmed by PCR nucleic acid detection. Bacterial infection: it was identified by pharyngeal secretion culture or blood culture.

Statistical analysis
The mean ± standard deviation or interquartile ranges was used to represent the characteristics of continuous variables. Frequency and percentage were used to describe the features of categorical variables. Student’s t-test was used to analyze the characteristics of continuous variables in two groups. Receiver operating characteristic (ROC) curves was used to assess sensitivity and specificity. P value less than 0.05 indicates statistical significance. All statistical analyses were performed by SPSS 24 software or GraphPad Prism V5.

RESULTS
General characteristics of subjects
A total of 291 children were collected for analysis. There were 36 cases of bacterial URTI, 197 cases of viral URTI and 58 cases of exanthem subitum. Fever is the common nonspecific symptom of acute URTI and exanthem subitum. Exanthem subitum have symptoms similar to acute URTI, such as runny nose (13.8%), pharyngeal congestion (29.3%), tonsil swelling (10.3%), mild dry cough (12.1%) (Table 1). The main pathogen of bacterial URTI is Streptococcus hemolyticus (Fig. 1). The main pathogens of viral URTI are influenza A virus and adenovirus.

Characteristics of β2-MG in viral and bacterial URTI
Compared with bacterial infection group, serum β2-MG level was higher in viral URTI and exanthem subitum (Fig. 2A and Table 2). Sensitivity and specificity were calculated and analyzed by GraphPad Prism V5 on November 4, 2020. The area under the curve (AUC) for β2-MG was 0.91 (95% CI [0.86–0.96]) for discriminating viral from bacterial URTI (Fig. 2B). When the concentration of β2-MG is 2.4 mg/L, the sensitivity to distinguish viral from bacterial infection is 81.2% (95% CI [75.1–86.4]%), and the specificity is 80.6% (95% CI [64.0–91.8]%). Adenovirus infection was similar to bacterial infection, most of which were characterized by increased white blood cell count and C-reactive protein (Table S1). For β2-MG, the AUC was 0.88 (95% CI [0.82–0.95]) for discriminating adenovirus...
Table 1  General characteristics of subjects.

| Characteristic                  | Upper respiratory tract infection | Exanthem subitum |
|--------------------------------|-----------------------------------|------------------|
|                                | Bacterial $n=36$                  | Viral $n=197$    | $n=58$           |
| Female, no. (%)                | 16(44.4)                          | 86(43.7)         | 22(37.9)         |
| Age Median (IQR), months       | 13(11,19)                         | 12(11,16)        | 13(10,15)        |
| Fever, no. (%)                 | 34(94.4)                          | 188(95.4)        | 58(100)          |
| Peak temperature (Mean ± SD), °C| 39.0 ± 0.6                        | 39.2 ± 0.5       | 39.5 ± 0.5       |
| Duration of fever (Mean ± SD), day | 3.6 ± 2.5                        | 3.4 ± 1.5        | 4.5 ± 1.1        |
| Febrile convulsion, no. (%)    | 4(11.1)                           | 31(15.7)         | 7(12.1)          |
| Eating less, no. (%)           | 9(25.0)                           | 44(22.3)         | 23(39.7)         |
| Runny nose, no. (%)            | 21(58.3)                          | 178(90.4)        | 8(13.8)          |
| Pharyngeal congestion, no. (%) | 36(100)                           | 197(100)         | 17(29.3)         |
| Swelling of tonsil, no. (%)    | 22(61.1)                          | 72(36.5)         | 6(10.3)          |
| Mild dry cough, no. (%)        | 2(5.6)                            | 28(14.2)         | 7(12.1)          |

Notes.
IQR, quartile range.

Figure 1  Pathogens of upper respiratory tract infection. In the cases of upper respiratory tract infection, there are 36 cases of bacterial infection and 197 cases of viral infection. The children’s ages range from 6 months to 24 months. The main pathogen of bacterial URTI is Streptococcus hemolyticus. The main pathogens of viral URTI are influenza A virus and adenovirus.

infection from bacterial infection (Fig. S1). β2-MG at cutoff 2.20 mg/L, the sensitivity to distinguish adenovirus infection from bacterial infection is 89.66% (95% CI [78.8–96.1]%), specificity is 72.2% (95% CI [54.8–85.8]%).
**Figure 2** β2-MG for identification of viral infection by ROC curve evaluation. (A) The distribution of serum levels of β2-microglobulin in bacterial URTI, viral URTI and exanthem subitem groups are shown by scatter plot. (B) ROC curves of β2-microglobulin levels for differentiating viral from bacterial URTI. The AUC for β2-microglobulin was 0.91 (95% CI [0.86–0.96]). (C) ROC curves of β2-microglobulin levels for distinguishing exanthem subitem from bacterial URTI. The AUC for β2-microglobulin was 0.99 (95% CI [0.98–1.00]). (D) ROC curves of β2-microglobulin levels for distinguishing exanthem subitem from viral URTI. The AUC for β2-microglobulin was 0.90 (95% CI [0.85–0.95]).

**Table 2** Difference of β2-MG in viral and bacterial infections.

| Variable            | N  | β2-microglobulin (mg/L) | P value   |
|---------------------|----|-------------------------|-----------|
| Bacterial URTI      | 36 | 1.92 ± 0.48             | reference |
| Viral URTI          | 197| 2.91 ± 0.65             | <0.001    |
| Exanthem subitem    | 58 | 4.19 ± 0.90             | <0.001    |

Notes.

URTI, upper respiratory tract infection

The AUC for β2-MG was 0.99 (95% CI [0.98–1.00]) for discriminating exanthem subitem from bacterial URTI (Fig. 2C). When the cutoff was 2.91 mg/L, the sensitivity of β2-MG to distinguish exanthem subitem from bacterial URTI was 94.8% (95% CI [85.6–98.9%]), and the specificity was 100% (95% CI [90.3–100%]).
Difference of $\beta$2-MG in exanthem subitum and virus URTI

The concentration of serum $\beta$2-MG in viral URTI and exanthem subitum was increased. Further statistical analysis, the level of $\beta$2-MG in exanthem subitum was significantly higher than that of viral URTI ($4.19 \pm 0.90$ mg/L vs $2.91 \pm 0.65$ mg/L, $P < 0.001$). The AUC for $\beta$2-MG was 0.90 (95% CI [0.85–0.95]) for discriminating exanthem subitum from viral URTI (Fig. 2D). When the cutoff was 3.40 mg/L, the sensitivity of $\beta$2-MG to distinguish exanthem subitum from viral URTI was 87.93% (95% CI [76.7–95.0]%), and the specificity was 84.3% (95% CI [78.4–89.1]%).

DISCUSSION

Through the analysis of the general characteristics of acute URTI and exanthem subitum, our results suggested that the clinical manifestations of some children with exanthem subitum were similar to acute URTI. Exanthem subitum may be difficult to distinguish from acute URTI before the rash appears. Although most of acute URTI are viral infections, there are also some bacterial infections (Hersh et al., 2013). Bacterial URTI requires antibiotic treatment. However, the overuse of antibiotics in children with acute upper respiratory tract infection is serious (Cheng et al., 2019; Kuchar et al., 2015; Trinh et al., 2020).

HHV-6 infection is the main cause of exanthem subitum (Agut, Bonnafous & Gautheret-Dejean, 2016). In addition, there is a small part of exanthem subitum is caused by HHV-7. Exanthem subitum only needs symptomatic treatment. Although the prognosis of exanthem subitum is benign, it is challenging to make a diagnosis before eruption. When the early persistent high fever can not be diagnosed in children with exanthem subitum, parents are anxious and reasonable treatment is facing challenges. Children with persistent high fever and without an apparent source are more likely to use unnecessary antibiotics before the viruses are identified (Colvin et al., 2012).

Identification of pathogens is helpful for early diagnosis of diseases. At present, there are some ways to identify pathogens. Culture is the most specific method to confirm pathogens infection, but it is low sensitivity, expensive and time-consuming (Agut, Bonnafous & Gautheret-Dejean, 2015). It has a long time span to diagnose pathogens by the change of serum antibody titer in acute phase and convalescent stage, which is suitable for retrospective diagnosis. PCR nucleic acid detection has high sensitivity and specificity, which is helpful to identify pathogens (Korman, Alikhan & Kaffenberger, 2017). However, the cost is expensive, so the PCR detection method has its limitations (Agut, Bonnafous & Gautheret-Dejean, 2015).

Acute URTI and exanthem subitum are common diseases in children. It is easy to identify pathogens in hospitals with advanced equipment. However, in the primary care hospitals, there is no perfect equipment for pathogen identification, especially PCR nucleic acid detection. In addition to pathogen detection, biomarker detection can also help to screen the categories of infectious pathogens. C-reactive protein and procalcitonin are used as bacterial biomarkers to identify bacterial infection and guide the use of antibiotics (Irwin et al., 2017; Katz, Sartori & Williams, 2019).

Is there viral biological indicator to identify viral infection and improve the accuracy of clinical diagnosis? $\beta$2-MG is a nonglycosylated protein (11.6 kDa) on the surface of...
almost all nucleated cells (Becker & Reeke Jr, 1985; Cunningham et al., 1973). β2-MG is a light chain of major histocompatibility complex class I, which plays a key role in adaptive immune system (Li, Dong & Wang, 2016; Wieczorek et al., 2017). Our results showed that the level of β2-MG in viral infection was significantly higher than that in bacterial infection. ROC curve analysis showed that β2-MG had high sensitivity and specificity in distinguishing viral from bacterial infection. This study was consistent with our previous study, and elevated β2-MG concentration might help to distinguish viral from bacterial infections in children with lower respiratory tract infection (Cai et al., 2020). The change of β2-MG level may be helpful in screening viral infection and avoiding antibiotic abuse. Another interesting result is that the level of β2-MG in children with exanthem subitum is significantly higher than that in children with viral URTI. We measured the concentration of β2-MG before the onset of rash in exanthem subitum. Therefore, this finding may help us to identify exanthem subitum early. We speculated that a significantly elevated serum β2-microglobulin level might indicate viral infection.

There are some limitations in this study. First, we only collected a small sample size of cases for study. Second, we only detected common pathogens, and did not exclude the combination of other undetectable pathogens, which would affect the results. Third, β2-MG detection has been routinely tested in clinic and is often used to assess renal function. The renal function of children is not mature until they were close to adults at 12 months old (Kearns et al., 2003). The challenge is that the effect of renal maturation on β2-MG needs further study.

CONCLUSIONS
Serum β2-MG may be a significant biological indicator in children with acute URTI and exanthem subitum. Whether β2-MG can be used as a biomarker of viral infection is worthy of further exploration. Further studies are needed to confirm the reliability of the results in more patients and infectious diseases.

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Competing Interests
The authors declare there are no competing interests.

Author Contributions
• Xulong Cai conceived and designed the experiments, analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.
Qiaolan Xu analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.

Chenrong Zhou, Tongjin Yin and Li Zhou performed the experiments, prepared figures and/or tables, and approved the final draft.

**Human Ethics**

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

This study was approved by the ethics committee of the Yancheng Third People’s Hospital (Approval Number: 2019100).

**Data Availability**

The following information was supplied regarding data availability:

Raw measurements are available in the Supplementary Files.

**Supplemental Information**

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.11109#supplemental-information.

**REFERENCES**

Agut H, Bonnafous P, Gautheret-Dejean A. 2015. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clinical Microbiology Reviews* 28:313–335 DOI 10.1128/CMR.00122-14.

Agut H, Bonnafous P, Gautheret-Dejean A. 2016. Human herpesviruses 6A, 6B, and 7. *Microbiology Spectrum* 4:1–18 DOI 10.1128/microbiolspec.DMIH2-0007-2015.

Arnež M, Avšič-Županc T, Uršič T, Petrovec M. 2016. Human herpesvirus 6 infection presenting as an acute febrile illness associated with thrombocytopenia and leukopenia. *Case Reports in Pediatrics* 2016:1–3 DOI 10.1155/2016/2483183.

Baugh KA, Tzannou I, Leen AM. 2018. Infusion of cytotoxic T lymphocytes for the treatment of viral infections in hematopoetic stem cell transplant patients. *Current Opinions in Infectious Diseases* 31:292–300 DOI 10.1097/qco.0000000000000456.

Becker JW, Reeke Jr GN. 1985. Three-dimensional structure of beta 2-microglobulin. *Proceedings of the National Academy of Sciences of the United States of America* 82:4225–4229 DOI 10.1073/pnas.82.12.4225.

Bellussi LM, Passali FM, Ralli M, De Vincentiis M, Greco A, Passali D. 2019. An overview on upper respiratory tract infections and bacteriotherapy as innovative therapeutic strategy. *European Review for Medical and Pharmacological Sciences* 23:27–38 DOI 10.26355/eurrev_201903_17345.

Cai X, Xu Q, Zhou C, Zhou L, Yong Q, Mu Q, Cheng Y, Wang J, Xie J. 2020. Distribution characteristics of serum β2-microglobulin between viral and bacterial lower respiratory tract infections: a retrospective study. *PeerJ* 8:e9814 DOI 10.7717/peerj.9814.
Cheng J, Chai J, Sun Y, Wang D. 2019. Antibiotics use for upper respiratory tract infections among children in rural Anhui: children’s presentations, caregivers’ management, and implications for public health policy. *Journal of Public Health Policy* **40**:236–252 DOI 10.1057/s41271-019-00161-w.

Colvin JM, Muenzer JT, Jaffe DM, Smason A, Deych E, Shannon WD, Arens MQ, Buller RS, Lee WM, Weinstock EJ, Weinstock GM, Storch GA. 2012. Detection of viruses in young children with fever without an apparent source. *Pediatrics* **130**:e1455–1462 DOI 10.1542/peds.2012-1391.

Cunningham BA, Wang JL, Berggård I, Peterson PA. 1973. The complete amino acid sequence of beta 2-microglobulin. *Biochemistry* **12**:4811–4822 DOI 10.1021/bi00748a001.

Das A, Trehan A, Bansal D. 2018. Risk Factors for microbiologically-documented infections, mortality and prolonged hospital stay in children with febrile neutropenia. *Indian Pediatrics* **55**:859–864 DOI 10.1007/s13312-018-1395-0.

David P, Megger DA, Kaiser T, Werner T, Liu J, Chen L, Sitek B, Dittmer U, Zelinskyy G. 2019. The PD-1/PD-L1 pathway affects the expansion and function of cytotoxic CD8(+) T cells during an acute retroviral infection. *Frontiers in Immunology* **10**:54 DOI 10.3389/fimmu.2019.00054.

Dien Bard J, Mongkolrattanothai K. 2019. Sepsis in children with febrile neutropenia. *The Journal of Applied Laboratory Medicine* **3**:530–533 DOI 10.1373/jalm.2018.028142.

Hattori F, Kawamura Y, Kozawa K, Miura H, Miyake M, Yoshikawa A, Ihira M, Yoshikawa T. 2019. Clinical characteristics of primary HHV-6B infection in children visiting the emergency room. *The Pediatric Infectious Disease Journal* **38**:e248–e253 DOI 10.1097/inf.0000000000002379.

Hersh AL, Jackson MA, Hicks LA, American Academy of Pediatrics Committee on Infectious D. 2013. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics* **132**:1146–1154 DOI 10.1542/peds.2013-3260.

Irwin AD, Grant A, Williams R, Kolamunnage-Dona R, Drew RJ, Paulus S, Jeffers G, Williams K, Breen R, Preston J, Appelbe D, Chesters C, Newland P, Marzouk O, McNamara PS, Diggle PJ, Carrol ED. 2017. Predicting risk of serious bacterial infections in febrile children in the emergency department. *Pediatrics* **140**:e20162853 DOI 10.1542/peds.2016-2853.

Katz SE, Sartori LF, Williams DJ. 2019. Clinical progress note: procalcitonin in the management of pediatric lower respiratory tract infection. *Journal of Hospital Medicine* **14**:688–690 DOI 10.12788/jhm.3301.

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. 2003. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *New England Journal of Medicine* **349**:1157–1167 DOI 10.1056/NEJMra035092.

Korman AM, Alikhan A, Kaffenberger BH. 2017. Viral exanthems: an update on laboratory testing of the adult patient. *Journal of the American Academy of Dermatology* **76**:538–550 DOI 10.1016/j.jaad.2016.08.034.
Kuchar E, Miskiewicz K, Szenborn L, Kurpas D. 2015. Respiratory tract infections in children in primary healthcare in Poland. Advances in Experimental Medicine and Biology 835:53–59 DOI 10.1007/5584_2014_34.

Langellotti CA, Gammella M, Soria I, Bellusci C, Quattrocchi V, Vermeulen M, Mongini C, Zamorano PI. 2020. An improved DNA vaccine against Bovine Herpesvirus-1 using CD40L and a chemical adjuvant induces specific cytotoxicity in mice. Viral Immunology 34:68–78 DOI 10.1089/vim.2020.0082.

Li L, Dong M, Wang XG. 2016. The implication and significance of beta 2 microglobulin: a conservative multifunctional regulator. Chinese Medical Journal 129:448–455 DOI 10.4103/0366-6999.176084.

Robert Kliegman JSG. 2019. Nelson textbook of pediatrics, 21e. Netherlands: Elsevier..

Stone RC, Micali GA, Schwartz RA. 2014. Roseola infantum and its causal human herpesviruses. International Journal of Dermatology 53:397–403 DOI 10.1111/ijd.12310.

Tang J, Chen J, He T, Jiang Z, Zhou J, Hu B, Yang S. 2019. Diversity of upper respiratory tract infections and prevalence of Streptococcus pneumoniae colonization among patients with fever and flu-like symptoms. BMC Infectious Diseases 19:24 DOI 10.1186/s12879-018-3662-z.

Trinh NTH, Bruckner TA, Lemaitre M, Chauvin F, Levy C, Chahwakilian P, Cohen R, Chalumeau M, Cohen JF. 2020. Association between National Treatment guidelines for upper respiratory tract infections and outpatient pediatric antibiotic use in France: an interrupted time-series analysis. Jornal de Pediatria 216:88–94 DOI 10.1016/j.jpeds.2019.09.017.

Wei X, Zhang Z, Walley JD, Hicks JP, Zeng J, Deng S, Zhou Y, Yin J, Newell JN, Sun Q, Zou G, Guo Y, Upshur REG, Lin M. 2017. Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China: a cluster-randomised controlled trial. The Lancet Global Health 5:e1258–e1267 DOI 10.1016/s2214-109x(17)30383-2.

Winston B. 2015. Upper respiratory tract infections. Pediatrics in Review 36:554–556 DOI 10.1542/pir.36-12-554.

Wieczorek M, Abualrous ET, Sticht J, Álvaro Benito M, Stolzenberg S, Noé F, Freund C. 2017. Major Histocompatibility Complex (MHC) Class I and MHC Class II proteins: conformational plasticity in antigen presentation. Frontiers in Immunology 8:292 DOI 10.3389/fimmu.2017.00292.

Zijlstra M, Bix M, Simister NE, Loring JM, Raulet DH, Jaenisch R. 1990. Beta 2-microglobulin deficient mice lack CD4-8+ cytolytic T cells. Nature 344:742–746 DOI 10.1038/344742a0.