JAMA Dermatology | Brief Report

Granulomatous Dermatitis Associated With Rubella Virus Infection in an Adult With Immunodeficiency

Bridget E. Shields, MD; Ludmila Perelygina, PhD; Sara Samimi, MD; Paul Haun, MD; Thomas Leung, MD, PhD; Emily Abernathy, MS; Min-hsin Chen, PhD; LiJuan Hao, MD; Joseph Icenogle, PhD; Beth Drolet, MD; Barbara Wilson, MD; Joshua S. Bryer, BA; Ross England, MD, PhD; Emily Blumberg, MD; Karolyn A. Wanat, MD; Kathleen Sullivan, MD, PhD; Misha Rosenbach, MD

IMPORTANCE Immunodeficiency-related, vaccine-derived rubella virus (RuV) as an antigenic trigger of cutaneous and visceral granulomas is a rare, recently described phenomenon in children and young adults treated with immunosuppressant agents.

OBJECTIVE To perform a comprehensive clinical, histologic, immunologic, molecular, and genomic evaluation to elucidate the potential cause of an adult patient's atypical cutaneous granulomas.

DESIGN, SETTING, AND PARTICIPANTS A prospective evaluation of skin biopsies, nasopharyngeal swabs, and serum samples submitted to the Centers for Disease Control and Prevention was conducted to assess for RuV using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and viral genomic sequencing. The samples were obtained from a man in his 70s with extensive cutaneous granulomas mimicking both cutaneous sarcoidosis (clinically) and $CD8^+$ granulomatous cutaneous T-cell lymphoma (histopathologically). The study was conducted from September 2019 to February 2021.

MAIN OUTCOMES AND MEASURES Identification and genotyping of a novel immunodeficiency-related RuV–associated granulomatous dermatitis.

RESULTS Immunohistochemistry for RuV capsid protein and RT-PCR testing for RuV RNA revealed RuV in 4 discrete skin biopsies from different body sites. In addition, RuV RNA was detected in the patient's nasopharyngeal swabs by RT-PCR. The full viral genome was sequenced from the patient's skin biopsy (RVs/Philadelphia.PA.USA/46.19/GR, GenBank Accession #MT249313). The patient was ultimately diagnosed with a novel RuV-associated granulomatous dermatitis.

CONCLUSIONS AND RELEVANCE The findings of this study suggest that clinicians and pathologists may consider RuV-associated granulomatous dermatitis during evaluation of a patient because it might have implications for the diagnosis of cutaneous sarcoidosis, with RuV serving as a potential antigenic trigger, and for the diagnosis of granulomatous cutaneous T-cell lymphoma, with histopathologic features that may prompt an evaluation for immunodeficiency and/or RuV.

JAMA Dermatol. 2021;157(7):842-847. doi:10.1001/jamadermatol.2021.1577
Published online May 26, 2021.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Bridget E. Shields, MD, Department of Dermatology, University of Wisconsin School of Medicine and Public Health, 600 Highland Ave, Madison, WI 53792 (bshields@dermatology.wisc.edu).

Immunodeficiency-related, vaccine-derived rubella virus (iVDRV) as an antigenic trigger of cutaneous and visceral granulomas has been rarely described primarily in pediatric patients have genetic immunosuppressive disorders or are receiving immunosuppressant agents.[1-3] To our knowledge, iVDRV has not been reported in adult patients, nor has wild-type rubella virus (RuV) been described as a trigger for RuV-associated cutaneous granulomatous dermatitis. We report a case of persistent RuV associated with granulomatous disease and explore the potential implications for the diagnosis of iVDRV-associated granulomatous dermatitis.

A man in his 70s with common variable immunodeficiency was evaluated for suspected cutaneous sarcoidosis. Common variable immunodeficiency was formally diagnosed with persistent hypogammaglobulinemia (IgG, IgA, and IgM) and recurrent sinopulmonary infections. He experienced gingivitis, periodontitis, skin, soft tissue, and bronchial infections. Immunoglobulin replacement therapy was begun when the patient was in his early 50s. Examination revealed diffuse violaceous plaques and nodules (**Figure 1**A and B), including involvement of surgical scars (Figure 1C). Initial skin biopsy revealed noncaseating granulomas and negative infectious stains, leading to a presumed diagnosis of sarcoidosis. The patient's disease had progressed over 9 years despite treatment with hydroxychloroquine, minocycline, doxycycline, oral corticosteroids, and methotrexate. He was referred to our institution for further management.

Infectious testing results for HIV, syphilis, and tuberculosis were negative. A second set of punch biopsies of samples from the affected skin was performed. The biopsies revealed a granulomatous dermatitis with CD8 T-cell predominance, histologically concerning for $CD8^+$ granulomatous cutaneous T-cell lymphoma (**Figure 2**). Flow cytometry failed to reveal an aberrant T-cell immunophenotype and T-cell receptor gene rearrangement was not clonal, ruling out lymphoma. Immunohistochemical staining for organisms remained negative.

Extensive diagnostic evaluation for extracutaneous granulomas was unrevealing. Immunoglobulin testing revealed persistently low IgG, IgA, and IgM levels consistent with the diagnosis of common variable immunodeficiency. Serum protein electrophoresis results were within reference ranges. Advanced lymphocyte and B cell panel testing further revealed a senescent T-cell compartment (eTable in the Supplement).[4-8] There was limited evidence of a T-cell defect, with $CD3^-$, $CD4^-$, and $CD8^-$ T-cell counts within the reference ranges (eTable in the Supplement). The patient

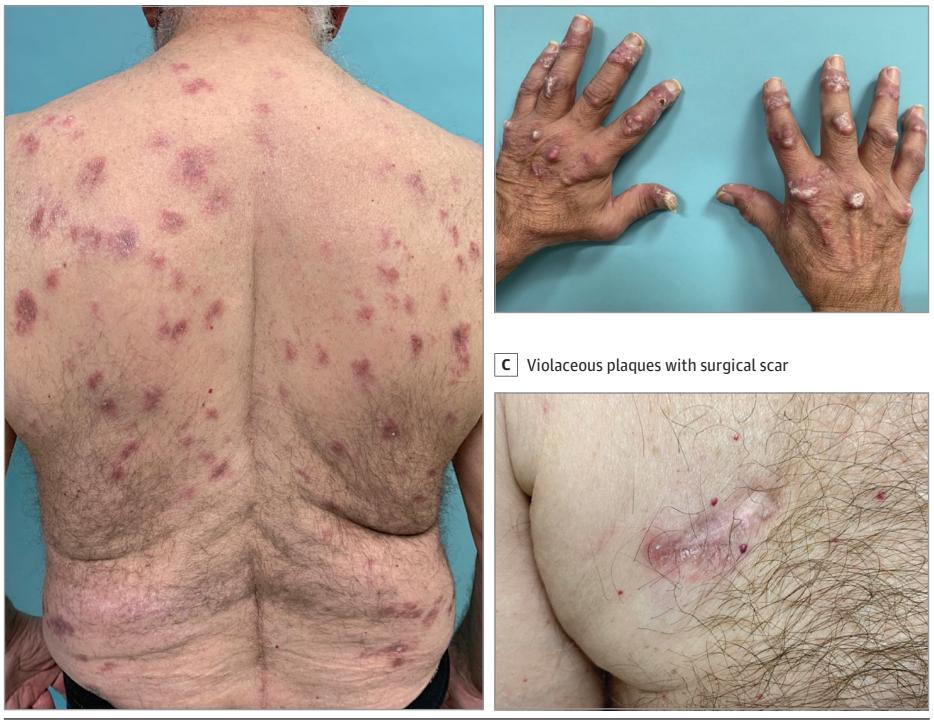
Key Points

Question Is there an identifiable antigenic trigger associated with clinically atypical, refractory cutaneous granulomas?

Findings In this case report, immunohistochemical and molecular analysis leading to the identification of a wildtype rubella virus strain was conducted in an immunocompromised man in his 70s initially diagnosed with sarcoidosis and treated with immunosuppressant agents.

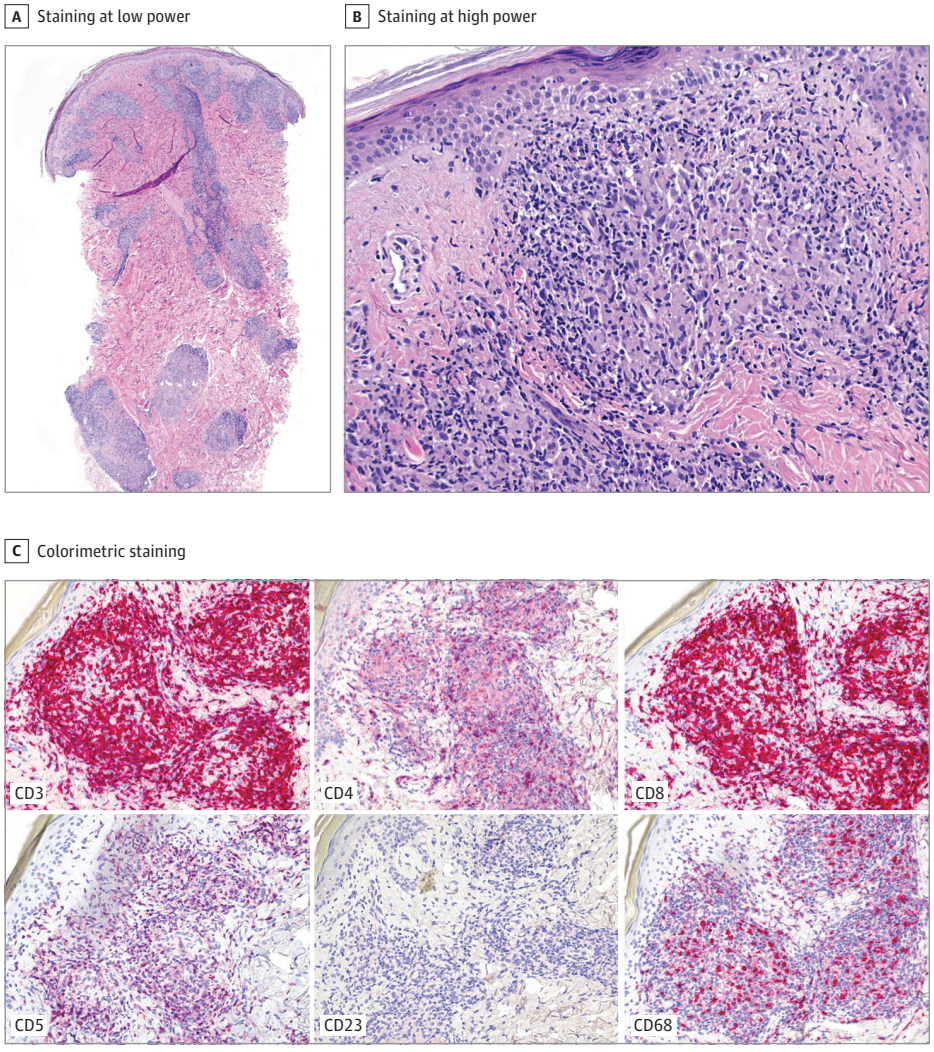
Meaning Immunodeficiency-related, rubella virus–associated granulomatous dermatitis may exist in adults.

Figure 1. Cutaneous Granulomas in the Patient



Violaceous plaques are spread diffusely on the back and trunk (A) with crusted hyperkeratotic nodules overlying the dorsal hands and fingers (B) and involvement of a surgical scar (C).

Figure 2. Histopathologic Examination and Immunohistochemical Staining of Cutaneous Granulomas



Low-power (A) and high-power (B) histologic examination of an older patient's dense granulomatous dermatitis with atypical lymphoid infiltrate (hematoxylin-eosin). Colorimetric immunohistochemical staining of the biopsy showing CD3, CD4, CD8, CD5, CD23, and CD68 lymphocytes (C). Involved lymphocytes highlighted with T-cell markers: CD3, CD5, and CD8. CD23 was largely negative and CD68 decorated histiocytes within granulomas. Original magnification ×40 in A, ×200 in B, and ×100 for all images in C.

had absent switched memory B cells but a total CD19 B cell count of 323 cells/μL, typical of patients with common variable immunodeficiency and granulomas or lymphoproliferation. He had CD8 T cells that were almost exclusively $CD28^-$, a feature associated with suppression of T-cell responses and chronic antigenic exposure.

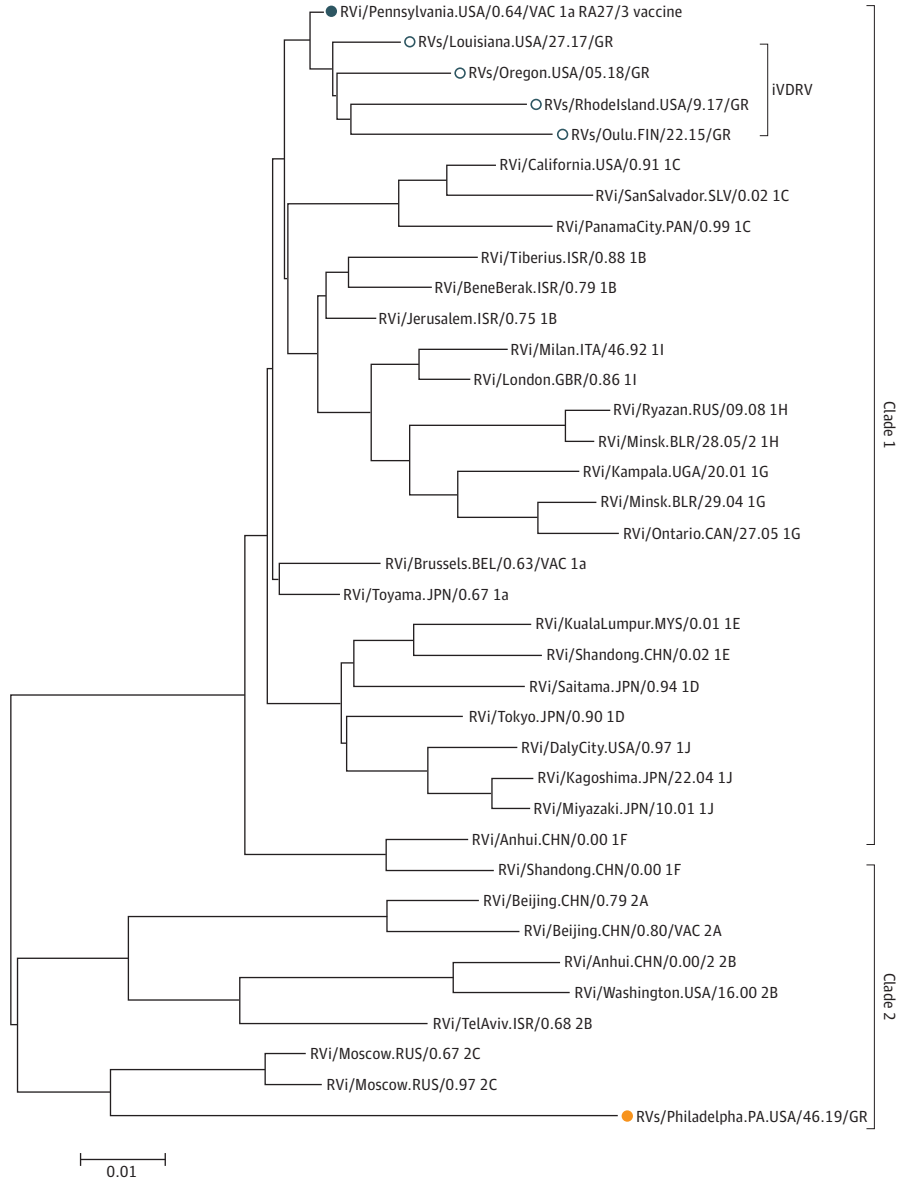
Methods

Given this patient's combination of immunodeficiency (eTable in the Supplement) and atypical clinical and histopathologic findings, additional skin biopsies, nasopharyngeal swabs, and serum samples were submitted to the Centers for Disease Control and Prevention to assess for RuV. All decisions were made by treating physicians for the care of this patient. The RuV RT-PCR detection and sequencing analysis from biopsy material was performed for the purpose of possible public health response as a part of ongoing CDC surveillance for rubella virus; this work was determined not to be research in humans by the CDC Institutional Review Board. This study was conducted September 2019 to February 2021.

Results

The patient's RuV IgM result was negative, RuV IgG titer was 60 IU/mL, and RuV 50% neutralization titer was 40. The presence of RuV antibody was attributed to his receipt of intravenous immunoglobulin. Immunohistochemistry for RuV capsid protein (eFigure in the Supplement) and real-time reverse-transcriptase polymerase-chain reaction (RT-PCR) testing for RuV RNA revealed RuV in 4 discrete skin biopsies of samples from different body sites. RuV RNA was also detected in the patient's nasopharyngeal swabs by RT-PCR, but isolation of RuV in cell culture from the skin biopsies and nasopharyngeal swabs was unsuccessful. The full viral genome was sequenced from the patient's skin biopsy sample (RVs/Philadelphia.PA.USA/46.19/GR,

Figure 3. Molecular Phylogenetic Analysis of Vaccine-Derived Rubella Virus (RuV) From the Patient's Skin Biopsy



The analysis involved 37 full genome nucleotide sequences of RuVs, World Health Organization reference viruses (n = 32); immunodeficiency-related, vaccine-derived rubella viruses (iVDRVs) (n = 4); and the patient's virus. The relationship of the patient's RuV to other known rubella viruses was inferred by using the maximum likelihood method based on the Tamura-Nei model. The scale bar indicates the number of base substitutions per site.

GenBank Accession #MT249313). The relationship of the patient's RuV to other known rubella viruses was inferred by using the maximum likelihood method based on the Tamura-Nei model.[9] Phylogenetic analysis (**Figure 3**) showed that the virus detected in this patient was not closely related to the live, attenuated RuV strain RA27/3, which is a part of the measles, mumps, and rubella vaccine (a clade 1, genotype 1a virus), but belonged to a clade 2 and was highly divergent (8.1%-11.6% nucleotide divergence) from the other known RuV sequences in a clade 2. A clade 2 virus has not been used as a vaccine in the US, suggesting a wild-type derived strain in our patient.

Discussion

The live, attenuated RuV strain RA27/3 is not known to persist in immunocompetent individuals, but altered cellular immunity may allow persistence and the development of cutaneous and visceral granulomas in immunocompromised hosts.[10] Previously reported cases of iVDRV-associated granulomatous eruptions have been described only in immunosuppressed pediatric patients and young adults.[1,2] It has recently been noted that RuV can persist in humans for many years, only to erupt as a chronic inflammatory process years to decades later.[10] The body sites

where RuV can persist are unknown, although persistence in epidermal keratinocytes and granuloma M2 macrophages in patients with primary immunodeficiencies has been described.[1] Disruption of immune control can be associated with resurgent viral replication and chronic inflammation of nearly any organ system, with the skin most commonly affected.[1]

There are 13 known RuV genotypes subdivided into 2 clades (1 and 2), with viruses of 4 genotypes (1E, 1G, 1J, and 2B) currently known to be the main genotypes of RuV circulating worldwide.[11] A wild-type RuV strain with an identical or closely related sequence to the strain in this patient is not known to be in global circulation. The patient described in this report was born in the US before 1957, which is the birth year for which presumptive evidence of natural immunity for persons born in the US is used.[12] Although we do not have direct evidence of exposure of this patient to RuV as a child, it is likely he was exposed during childhood (ie, born before 1957). Circulation of a clade 2 virus before 1957 has not been documented in the US, but the number of RuV sequences in the US before 1966 is limited.[1] The patient traveled extensively in Europe as an adult where clade 2 viruses were present in some of the countries he visited, and it is possible that he was infected in a country other than the US.[1] A conclusion as to the source of RuV in this patient is impossible.

Limitations

This report has limitations. Although RuV capable of replication in cell cultures was not obtained from this patient's specimens, there remained the possibility that a wild-type-derived RuV strain capable of replication in humans was present in these specimens, raising concerns for risk of transmission, particularly to unvaccinated people, pregnant women, infants, or immunocompromised individuals. Although multiple specimens were analyzed, all samples came from a single patient.

Conclusions

This case represents the identification of a novel, wild-type RuV strain in an immunocompromised adult initially diagnosed with and treated for sarcoidosis. This case has potential implications for the diagnoses of cutaneous sarcoidosis, granulomatous cutaneous T-cell lymphoma, and other cutaneous granulomatous diseases. There may be a subset of patients with subclinical immune dysregulation and persistent RuV-triggered granulomatous disease who are misdiagnosed with one of the above entities. This patient's cutaneous granulomatous disease continued to worsen after RuV identification; ribavirin therapy was initiated, resulting in notable improvement. Clinicians and pathologists may use the knowledge of this entity in patients presenting with atypical cutaneous granulomas, both clinically and on histopathologic testing.

ARTICLE INFORMATION

Accepted for Publication: April 3, 2021.

Published Online: May 26, 2021. doi:10.1001/jamadermatol.2021.1577

Author Affiliations: Department of Dermatology, University of Wisconsin School of Medicine and Public Health, Madison (Shields, Drolet); Assistant Section Editor, *JAMA Dermatology* (Shields); Centers for Disease Control and Prevention, Division of Viral Diseases, Atlanta, Georgia (Perelygina, Abernathy, Chen, Hao, Icenogle); Department of Dermatology, University of Pennsylvania Perelman School of Medicine, Philadelphia (Samimi, Haun, Leung, Bryer, Rosenbach); Department of Dermatology, Medical College of Wisconsin, Milwaukee (Wilson, Wanat); Division of Infectious Diseases, University of Pennsylvania Perelman School of Medicine, Philadelphia (England, Blumberg); Section Editor, *JAMA Dermatology* (Wanat); Division of Allergy and Immunology, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Sullivan); Division of Allergy and Immunology, University of Pennsylvania Perelman School of Medicine, Philadelphia, (Sullivan).

Author Contributions: Drs Shields and Rosenbach had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Sullivan and Rosenbach contributed equally to this study.
Concept and design: Shields, Perelygina, Haun, Icenogle, Drolet, Wilson, England, Blumberg, Sullivan, Rosenbach.
Acquisition, analysis, or interpretation of data: Shields, Perelygina, Samimi, Haun, Leung, Abernathy, Chen, Hao, Icenogle, Bryer, England, Wanat, Sullivan, Rosenbach.
Drafting of the manuscript: Shields, Samimi, Icenogle, Sullivan.
Critical revision of the manuscript for important intellectual content: Shields, Perelygina, Haun, Leung, Abernathy, Chen, Hao, Icenogle, Drolet, Wilson, Bryer, England, Blumberg, Wanat, Rosenbach.
Administrative, technical, or material support: Shields, Perelygina, Samimi, Haun, Abernathy, Chen, Hao, Icenogle, Drolet, Bryer, England, Wanat, Sullivan, Rosenbach.
Supervision: Shields, Leung, Icenogle, Drolet, Wanat, Rosenbach.

Conflict of Interest Disclosures: Dr Haun reported receiving royalties from Karger Inc and serving as a paid member of the advisory board for Kyowa Kirin. Dr Rosenbach reported receiving personal fees from Merck Consulting: Drug Reactions, grants from Processa Research; consulting fees from necrobiosis lipoidica trial planning, Janssen Pharmaceuticals, and Eli Lilly outside the submitted work. No other disclosures were reported.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention. Dr Shields is an Assistant Section Editor of *JAMA Dermatology*, but she was not involved in any of the decisions regarding review of the manuscript or its acceptance. Dr Wanat is a Section Editor of *JAMA Dermatology*, but she was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Additional Contributions: We thank the patient for granting permission to publish this information.

REFERENCES

1. Perelygina L, Plotkin S, Russo P, et al. Rubella persistence in epidermal keratinocytes and granuloma M2 macrophages in patients with primary immunodeficiencies. *J Allergy Clin Immunol*. 2016;138(5):1436-1439.e11. doi:10.1016/j.jaci.2016.06.030

2. Bodemer C, Sauvage V, Mahlaoui N, et al. Live rubella virus vaccine long-term persistence as an antigenic trigger of cutaneous granulomas in patients with primary immunodeficiency. *Clin Microbiol Infect*. 2014;20(10):O656-O663. doi:10.1111/1469-0691.12573

3. Dhossche J, Johnson L, White K, et al. Cutaneous granulomatous disease with presence of rubella virus in lesions. *JAMA Dermatol*. 2019;155(7):859-861. doi:10.1001/jamadermatol.2019.0814

4. Valiathan R, Deeb K, Diamante M, Ashman M, Sachdeva N, Asthana D. Reference ranges of lymphocyte subsets in healthy adults and adolescents with special mention of T cell maturation subsets in adults of South Florida. *Immunobiology*. 2014;219(7):487-496. doi:10.1016/j.imbio.2014.02.010

5. Fagnoni FF, Vescovini R, Mazzola M, et al. Expansion of cytotoxic $CD8^+$ $CD28^-$ T cells in healthy ageing people, including centenarians. *Immunology*. 1996;88(4):501-507. doi:10.1046/j.1365-2567.1996.d01-689.x

6. Azuma M, Phillips JH, Lanier LL. $CD28^-$ T lymphocytes.: antigenic and functional properties. *J Immunol*. 1993;150(4):1147-1159.

7. Morbach H, Eichhorn EM, Liese JG, Girschick HJ. Reference values for B cell subpopulations from

infancy to adulthood. *Clin Exp Immunol*. 2010;162 (2):271-279. doi:10.1111/j.1365-2249.2010.04206.x

8. Qin L, Jing X, Qiu Z, et al. Aging of immune system: Immune signature from peripheral blood lymphocyte subsets in 1068 healthy adults. *Aging (Albany NY)*. 2016;8(5):848-859. doi:10.18632/aging.100894

9. Tamura K, Nei M. Estimation of the number of nucleotide substitutions in the control region of mitochondrial DNA in humans and chimpanzees. *Mol Biol Evol*. 1993;10(3):512-526.

10. Perelygina L, Chen MH, Suppiah S, et al. Infectious vaccine-derived rubella viruses emerge, persist, and evolve in cutaneous granulomas of children with primary immunodeficiencies. *PLoS Pathog*. 2019;15(10):e1008080. doi:10.1371/journal.ppat.1008080

11. Rivailler P, Abernathy E, Icenogle J. Genetic diversity of currently circulating rubella viruses: a need to define more precise viral groups. *J Gen Virol*. 2017;98(3):396-404. Figure Legends. doi:10.1099/jgv.0.000680

12. Centers for Disease Control and Prevention. Routine measles, mumps, and rubella vaccination. Updated January 26, 2021. Accessed January 4, 2020. https://www.cdc.gov/vaccines/vpd/mmr/hcp/recommendations.html