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in Military Service Members

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13. ABSTRACT (Maximum 200 Words) Background: In response to threats of bioterrorism, US military personnel began receiving smallpox vaccinations in 2003. Although some adverse health effects associated with smallpox vaccination are well described, much less has been documented about reproductive health outcomes. Smallpox vaccine, as a live-virus product, has caused fetal vaccinia in rare cases when given in pregnancy. The potential for the product to cause pregnancy loss, birth defects, or other birth problems has not been as well documented, especially in the recent era. Objectives: To describe the incidence and prevalence of adverse reproductive health outcomes among military service members who received smallpox vaccination. Research Methods: Electronic birth records are accessed directly from the Standard Inpatient Data Record (SIDR), Standard Ambulatory Data Record (SADR), Health Care Service Record (HCSR); immunization data are obtained from the Defense Eligibility and Enrollment System (DEERS). All data are accessed through formal agreements established by the DoD Birth and Infant Health Registry. Using these data, adverse reproductive health outcomes are assessed, including birth defects, pregnancy loss, and infertility among military families exposed to smallpox vaccine.				
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INTRODUCTION

In response to perceived threats of biological weapons use by terrorists and rogue nations, the United States Food and Drug Administration (US FDA) approved the use of smallpox vaccine in October 2002. The US Department of Defense (DoD) established the Smallpox Vaccination Program for selected military personnel on 13 December 2002.(1) The vaccine approved by the FDA, Dryvax®, was first approved in 1931, and current stocks were produced by Wyeth Laboratories in the late 1970s to early 1980s. Because this vaccine was administered to billions of individuals over nearly half a century, the short-term adverse health events associated with the vaccine are fairly well documented.(2)

Although there is an adequate body of scientific literature on the adverse health effects associated with smallpox vaccination, much less has been reported concerning reproductive health. As a live virus product, smallpox vaccine has resulted in fetal vaccinia when given to pregnant women. This perinatal infection most often results in pregnancy loss or neonatal death; the risk of fetal vaccinia occurring after smallpox vaccination is estimated at 1/10,000 to 1/100,000.(3-7) No fetal vaccinia cases were observed among more than 4000 pregnant women vaccinated against smallpox in New York City in 1947.(8)

The risk of pregnancy loss, in the absence of fetal vaccinia, is less well established. While some large reviews reassure that no increased risk exists,(3,8,9) other small reports have cited concern that smallpox vaccination can cause spontaneous abortion.(10-12) Surveillance for pregnancy loss is always challenging because early pregnancies are difficult to recognize, losses may have multiple etiologies, and etiology is rarely established.(13-15) Likewise, risk factors for reduced fertility in relation to vaccination exposures can be extremely difficult to evaluate epidemiologically.(16-17) Large population-based studies, evaluating consistent and complete data sources are required to describe exposures associated with such outcomes.(18)

At least as concerning as pregnancy loss, an increased risk of birth defects can be extraordinarily alarming to prospective parents. Smallpox vaccination given during pregnancy has been associated with birth defects, specifically club foot malformations, in only one review in the 1970s.(19) These findings from Iran have been dismissed by many because they are not reproduced in other studies, and perhaps were associated with a vaccinia formulation that differs from the US Dryvax®.(20) Still others contend that live virus vaccines like smallpox, given during pregnancy, can plausibly cause birth defects.(21-24)

The risk for adverse reproductive health outcomes after exposures to non-pregnant women or men may be less biologically plausible than exposures to pregnant women, relying on delayed effects on germ cells. Given many unknowns about causation, the difference in plausibility does not necessarily make such exposures less concerning to families. Exposures associated with birth defects, in particular, remain an extraordinarily challenging issue for families, reproductive health researchers, and policymakers. In the US military, deployment to wars and associated military-unique exposures have caused great concern and resource-intensive research that assess later appearance of birth defects in children.(25-31)

Currently, with the exception of the passive Vaccine Adverse Events Reporting System (VAERS) for short-term outcomes,(32) there is no structured system to evaluate reproductive health effects of vaccinations.(33) The US military, charged with maintaining the health of all service members and their families, and with a growing population of women members,(34) has recently developed a strong surveillance system for birth defects.(35,36) This system has been applied in a judicious way to evaluate alleged associations between anthrax vaccination and birth defects, and has developed strong methodology and data validation protocols.(37,38) We are using this system to address the challenging questions surrounding potential associations between smallpox vaccine and adverse reproductive health outcomes.

BODY OF REPORT

Methods are described in the protocol.

The project began and continues to collect and process both immunization and birth data. Immunization records have been extracted from the DEERS Active Duty Immunization datasets. These data are complete through

December 2003. In January 2005, the second in the series of seven extractions will be downloaded for the period 1 January through June 30, 2004.

Preliminary extractions have aggregated DoD dependent birth records for the Birth and Infant Health Registry from TriCare SIDR, SADR and HCSR tables through December 2003. The next scheduled extractions will occur in January 2005.

Results will be reported following data collection and analyses.

KEY RESEARCH ACCOMPLISHMENTS

Awaiting completion of data collection and analyses

REPORTABLE OUTCOMES

There are no reportable outcomes at this time.

CONCLUSIONS

Data collection continues. Analyses, results and conclusions are pending, as above.

REFERENCES

1. The Smallpox Vaccination Program, Resource Center: Policies, Under Secretary of Defense, Personnel and Readiness, Policy on Administrative Issues Related to Smallpox Vaccination Program (SVP), 13 December 2002. Available at <http://www.smallpox.army.mil/resources/policies.asp>.
2. Centers for Disease Control and Prevention. Vaccinia (smallpox) vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2001;50(RR10);1-25.
3. Suarez VR, Hankins GD. Smallpox and pregnancy: from eradicated disease to bioterrorist threat. Obstet Gynecol 2002;100(1):87-93
4. Levine MM. Live-virus vaccines in pregnancy: risks and recommendations. Lancet 1974;2:34--8.
5. Lane JM, Millar JD, Neff JM. Smallpox and smallpox vaccination policy. Ann Rev Med 1971;22:251-72.
6. Weilenga G, van Tongeren HA, Ferguson AH, van Fijessel TG. Prenatal infection with vaccinia virus. Lancet 1961;1:258-60.
7. Green DM, Reid SM, Rhaney K. Generalized vaccinia in the human foetus. Lancet 1966;1:1296.
8. Greenberg M, Yankauer A, Krugman S, Osborn JJ, Ward RS, Dancis J. Effect of smallpox vaccination during pregnancy on the incidence of congenital malformations. Pediatrics 1949;3:456.
9. Engstrom L. Smallpox vaccination during pregnancy. Act Med Scand Suppl 1966;464:139-46
10. MacArthur P. Congenital vaccinia and vaccinia gravidarum. Lancet 1952;12:1104-6
11. Saxen L, Cantell K, Hakama M. Relation between smallpox vaccination and outcome of pregnancy. AJPH Nations Health 1968;58(10)1910-21.
12. Luisi M. Smallpox vaccination and pregnancy. Am J Obstet Gynecol 1977;128(6):700

13. Garcia-Enguidanos A, Calle ME, Valero J, Luna S, Dominguez-Rojas V. Risk factors in miscarriage: a review. *Eur J Obstet Gynecol Reprod Biol* 2002;102(2):111-9
14. Ellish NJ, Saboda K, O'Connor J, Nasca PC, Stanek EJ, Boyle C. A prospective study of early pregnancy loss. *Hum Reprod* 1996;11(2):406-12
15. Boyles SH, Ness RB, Grisso JA, Markovic N, Bromberger J, CiFelli D. Life event stress and the association with spontaneous abortion in gravid women at an urban emergency department. *Health Psychol* 2000;19(6):510-4
16. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril* 2003;79(3):577-84
17. Hjollund NH, Jensen TK, Bonde JP, Henriksen TB, Andersson AM, Kolstad HA, Ernst E, Giwercman A, Skakkebaek NE, Olsen J. Distress and reduced fertility: a follow-up study of first-pregnancy planners. *Fertil Steril* 1999;72(1):47-53
18. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. *J Infect Dis* 1970;122:303-9.
19. Naderi S. Smallpox vaccination during pregnancy. *Obstet Gynecol.* 1975;46(2):223-6.
20. US Department of Defense. Information Paper on Pregnancy Discovered after Smallpox Vaccination. DASG-HCA Apr 2003. Accessed at <http://www.smallpox.army.mil/media/pdf/pregnancyinfopaper.pdf>
21. Harley JD, Gillespie AM. A complicated case of congenital vaccinia. *Pediatrics* 1972;50:150.
22. Hanshaw JB, Dudgeon JA. Evidence for the viral etiology of congenital defects. *Major Problems in Clinical Pediatrics* 1978;17:10-6
23. Apuzzio J, Ganesh V, Iffy L, Al-Khan A. Varicella vaccination during early pregnancy: a cause of in utero miliary fetal tissue calcifications and hydrops? *Infect Dis Obstet Gynecol* 2002;10(3):159-60
24. Yazbak FE, Yazbak K. Live virus vaccination near a pregnancy: flawed policies, tragic results. *Med Hypotheses* 2002;59(3):283-8
25. Briggs J. The tiny victims of Desert Storm. *Life*. November 1995:46-61.
26. Moehringer JR. Legacy of worry. *Los Angeles Times*. October 24, 1995:A1,3.
27. Cowan DN, DeFraitres RF, Gray GC, Boldenbaum MB, Wishik SM. The risk of birth defects among children of Persian Gulf War veterans. *N Engl J Med* 1997;336:1650-6.
28. Aschengrau A, Monson RR. Paternal military service in Vietnam and the risk of late adverse pregnancy outcomes. *Am J Public Health* 1990;80(10):1218-24.
29. Erickson JD, Mulinare J, McClain PW, Fitch TG, James LM, McClearn AB, Adams MJ Jr. Vietnam veterans' risks for fathering babies with birth defects. *JAMA* 1984;252(7):903-12.
30. Kang HK, Mahan CM, Lee KY, Magee CA, Mather SH, Matanoski G. Pregnancy outcomes among U.S. women Vietnam veterans. *Am J Ind Med* 2000;38(4):447-54.
31. Araneta MRG, Schlangen KM, Edmonds LD, Destiche DA, Merz RD, Hobbs CA, Flood TJ, Harris JA, Krishnamurti D, Gray GC. Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993. *Birth Defects Research (Part A)* 2003;67:246-60.

32. Singleton JA, Lloyd JC, Mootrey GT, Salive ME, Chen RT. An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system. VAERS Working Group. *Vaccine* 1999;17(22):2908-17
33. Verdier F, Barrow PC, Burge J. Reproductive toxicity testing of vaccines. *Toxicology* 2003;185(3):213-9
34. United States Department of Defense Directive 5136.1-P, Medical Readiness Strategic Plan: 1998–2004. 1998, Washington, DC.
35. Assistant Secretary of Defense for Health Affairs. Policy for national surveillance for birth defects among Department of Defense health care beneficiaries. 1998, Washington, DC.
36. Ryan MAK, Pershyn-Kisor MA, Honner WK, Smith TC, Reed RJ, Gray GC. The Department of Defense Birth Defects Registry: overview of a new surveillance system. *Teratology* 2001; 64(S1):S26-9
37. Institute of Medicine. The anthrax vaccine: Is it safe? Does it work? ISBN 0-309-08339-7; 2002. National Academy Press: Washington, DC
38. Centers for Disease Control and Prevention. Notice to Readers: Status of U.S. Department of Defense Preliminary Evaluation of the Association of Anthrax Vaccination and Congenital Anomalies. *MMWR* 2002;51(06):127

BIBLIOGRAPHY OF RELATED RESEARCH PRODUCTS

Napolitano PG, Ryan MAK, Grabenstein JD. Pregnancy discovered after smallpox vaccination: Is vaccinia immune globulin appropriate? *Am J Obstet Gynecol* 2004;191(6):1863-7.

Ryan M, Grabenstein JD, Broder K. Women with smallpox vaccine exposure during pregnancy reported to the National Smallpox Vaccine in Pregnancy Registry - United States, 2003. *MMWR* 2003;52(17):386-8. Reprinted in *Infectious Diseases in Children* 2003;16(6):16.

Ryan M, Aran R, Campbell K, Chow S, Conlin A, Strickler J, Kenyan K, Seward J, Cano M, Mulinare J, Napolitano P, Pierce B, Engler R, Grabenstein J. The National Smallpox Vaccine in Pregnancy Registry: Update on Women Inadvertently Exposed to Smallpox Vaccine and Their Early Pregnancy Outcomes. National Center on Birth Defects and Developmental Disabilities Conference, July 26-28, 2004, Washington, DC.

Ryan M, Seward J, Rudy C, Chow S, Stiegman V, Strickler J, Conlin A, Kenyan K, Santos S, Mulinare J, Grabenstein J. The National Smallpox Vaccine in Pregnancy Registry: An Interim Report. Presented to the Advisory Committee on Immunization Practices, 23-24 Jun 2004, Atlanta, GA.

Aran R, Ryan M, Alexander B, Campbell K, Grabenstein J, Napolitano P, Pierce B, Engler R, Seward J, Mulinare J. The National Smallpox Vaccine in Pregnancy Registry. 43rd Annual Teratology Society Meeting, Jun 21-26, 2003, Philadelphia, PA. Also presented at the American College of Obstetricians and Gynecologists 2003 Armed Forces District Meeting, Oct 19-22, 2003, San Antonio, TX.