

Meningitis in the Sahel: Burkina Faso's 2008 Epidemic and the Meningitis Vaccine Project

Aaron Kofman

Introduction

Meningococcal meningitis, caused by the bacterium *Neisseria meningitidis*, is a devastating disease that is responsible for infecting over 500,000 people worldwide every year. Triggered by several different types of bacteria and viruses which infect the thin lining between the blood and spinal cord called the meninges, meningitis can range in severity from a mild headache, fever, and vomiting in the viral case to brain damage, haemorrhagic rash, loss of circulation, and death in the bacterial case. The greatest burden of bacterial meningitis worldwide occurs in the Sahel region of sub-Saharan Africa, a strip of countries from Senegal to Ethiopia that has been dubbed "the meningitis belt" for the yearly meningitis epidemics that rapidly spread throughout the region. Containing some of the world's most vulnerable populations, the Sahel has been at the center of the international meningitis response for decades, with major controversies over both the best vaccine and intervention strategy raging among medical professionals to this day.

While all countries across the Sahel experience some degree of meningitis, few are impacted as strongly every year as Burkina Faso. In 1996, 4,000 deaths were reported in Burkina Faso when the largest meningitis epidemic ever recorded in Africa spread to kill over 20,000 people. A small, landlocked country with a population of approximately 15 million, it ranks seventh from the bottom on the UNDP's Human Development Index. While all countries in the belt experience some degree of meningitis flare-up during the dry season, large epidemics usually only take place every 6 to 12 years. Thanks to a perfect storm of climatological, epidemiological, and infrastructural conditions, Burkina Faso is ravaged by epidemics every single year. After examining meningococcal meningitis at a biological and epidemiological level, this article explores the challenges involved in vaccination in Burkina Faso and assesses the current Meningitis Vaccine Project (MVP)'s efficacy in stemming the tide of the disease.

Epidemiology of Meningococcal Meningitis in Burkina Faso:

While the vast majority of *N. meningitidis* is commensal with its human host, the bacteria becomes invasive it can cause onset of the disease within 4 days of acquisition on average (in a range of 2 to 10 days). Most patients are hospitalized within 24 hours of onset of illness, and of these 10-15% will die, even with antibiotic treatment. 5-10% of patients will die within the initial 24-hour period. The brief latency period and fast symptomatic period make control measures immensely difficult as the epidemic will often sweep through a region before containment is possible. Though it is still unclear as to what factors trigger invasiveness, a recent study in 2005 implicated an 8-kb bacteriophage DNA (prophage) as the causative agent behind meningococcal invasiveness. Though few studies have followed up on this theory, it appears to provide a plausible explanation for why a relatively small percentage of meningococci become invasive.

Invasive and non-invasive meningococcus alike take advantage of a number of vulnerabilities of their human hosts at both the household and community levels. At the household level, family members who share bedrooms with an infected person are at risk to inhale infected respiratory droplets. The infection can also easily spread with the aid of cooking fire smoke, which damages the mucosa of the nasopharynx and creates an opportunity for meningococcal colonization. As many kitchens in Sahelian households are poorly ventilated, smoke from firewood stoves is more easily trapped and inhaled by household members. Over time, accumulated damage to the nasopharyngeal mucosa makes family members vulnerable to meningococcal colonization. For communities, the role of household smoke is played on the larger scale by the dry climate from February to May in the Sahel. During these months, low humidity and dust blown by wind causes desiccation within the oral cavity and inhibits the defense mechanism of the mucosa,

Background: Meningitis Vaccines

Meningitis vaccines can be divided into two categories. The first type of vaccine contains purified polysaccharide antigen capsules specific to various combinations of *N. meningitidis* serogroups A, B, C, Y, and/or W-135. The first such vaccine was developed in the 1960s and contained polysaccharide antigens specific to serogroups A and C. Since the bulk of meningitis in the Sahel was serogroup A, the vaccine was distributed widely in Africa, as well as in Europe and Asia, which had a high prevalence of serogroup C. Today, the vaccine is available for \$0.66 per dose and is the most popular meningitis vaccine in the Sahel due to its low cost. In the 1980s, in response to the call for a vaccine that would recognize more serogroups, a tetravalent polysaccharide vaccine was developed against serogroups A, C, Y, and W135 (licensed by both Sanofi and GlaxoSmithKline in the early 1980s) and is also in use in Africa. A special, low-cost (\$1.50/dose) trivalent polysaccharide vaccine against serogroups A, C, and W-135 was also created specifically for use in Africa by GSK in 2002 in response to the growing need for immunity against W-135 meningitis (but not the Y serogroup). Still, despite the low cost of the trivalent vaccine the bivalent version is most widely used due to its lower cost and, up until recently, the lack of a need for W-135 immunity.


A second type of meningitis vaccine was developed in the 1980s that chemically conjugated a protein to the capsular polysaccharide antigen. This vaccine was primarily developed in response to the poor results of the polysaccharide vaccine in children, who did not confer immunity from the vaccine as well as adults. Conjugate vaccines provide longer-lasting immunity than polysaccharide vaccines and in particular reduce transmission of bacteria dramatically, providing herd immunity. Licensed in 2005, the tetravalent vaccine confers immunity against serogroups A, B, C, and W135 by conjugating the diphtheria toxoid protein with the polysaccharide antigen. Though highly effective, the vaccine is currently only in use in the United States due to its high cost (\$100/dose). The Meningitis Vaccine Project (MVP) was set up with funding from the Gates Foundation in 2001, with the goal of providing a cheap, monovalent serogroup A conjugate vaccine with tetanus toxoid for use in the meningitis belt. Though still under development, the vaccine is expected to be made available within a year or two and is anticipated to significantly reduce the meningitis burden throughout the Sahel.

leaving them more vulnerable to colonization by invasive meningococcus. The impact of stronger winds during the winter months are also a major factor in transmitting the meningococcus through air across vast distances.

Of the yearly outbreaks of meningitis in Burkina Faso, 1959, 1970, 1984, 1987 and 1996 were the most devastating, with the 1996 epidemic claiming over 4,000 lives. These epidemics were all of serogroup A meningococcal meningitis; until 2001, cases of W135 meningitis were found only rarely. Depending on the severity of the yearly meningitis epidemics, the mortality rate from the disease can range from below 10% to 13%. In 2001 and 2002, two large outbreaks that killed 1900 and 1200 (respectively) in Burkina Faso, were confirmed to be caused by *N. meningitidis* of serogroup W-135, and were subsequently linked to the W-135 meningitis outbreak in Saudi Arabia among Hajj pilgrims in 2000. As the first major W-135 outbreaks in the Sahel, the outbreaks prompted

fears of a massive W-135 epidemic since the vast majority of vaccines being used in the epidemic response strategy were bivalent A/C polysaccharide. Since then, however, serogroup A has re-emerged in epidemics in Burkina Faso and has also been implicated in the 2001-2002 epidemics along with W-135. While the future epidemiology of these serogroups is unclear, it is certain that W-135 will play a larger role than it has in the past.

In 2008, a new epidemic began to unfold in fourteen districts in Burkina Faso. Five of these districts – including Reo Tinto in the west, Boulsa and Titao in the north, and Sig-nonghin in the center near the capital, Ouagadougou – were declared epidemic zones as 3,181 cases were identified from January through March and 366 people died. Within that time period, only two zones were downgraded after vaccination campaigns – evidence, perhaps, of the limited reach of the epidemic response strategy in multiple regions. Even more



disturbingly, one month later, a new report emerged identifying meningitis cases in regions that had been previously vaccinated.³ As the number of deaths rose to over 700, teams of WHO and CDC investigators flew into Burkina Faso to investigate what went wrong. One possibility was that the outbreak was caused by the W135 strain, while the previously vaccinated population had only received the bivalent A/C vaccine. If not, had they received the tetravalent A, C, Y, W-135 vaccine (“Menomune”), which had been recalled in 2002 due to loss of serogroup A potency? Had enough people been vaccinated within these regions to confer herd immunity upon the whole population? Could they even be sure that the infecting organism was *N. meningitidis*? Before any of these questions could be answered definitively, over 900 people had been killed in Burkina Faso.

Immediately following the outbreak, the WHO and CDC sent a team of outbreak specialists to determine what went wrong. Over a year later, no report has been made public, although the official response from the CDC was that a report had recently been submitted to the Ministry of Health in Burkina Faso and was under review. Until the details of the report are known, we can only speculate as to the true cause of the epidemic. Given that a number of epidemic regions close to the “previously vaccinated” regions were serogroup A, the evidence suggests that the epidemic was also serogroup A in these regions. If that were the case, people who were previously vaccinated must have been vaccinated with tetravalent A, C, Y, W-135 polysaccharide vaccine, since patients receiving polysaccharide vaccine are supposed to be immune for three years and no issues were reported with the bivalent vaccine (aside from skepticism among advocates of epidemic response that it is effective in children). Though a CDC official suggested that those affected had likely lost immunity, these patients had been vaccinated within three years – so all clues point to use of tetravalent Menomune that had lost serogroup A potency.

The Meningitis Vaccine Project

With both the polysaccharide vaccine and the epidemic response strategy’s efficacy in question, the

greatest hope for meningitis treatment and prevention lies with the Meningitis Vaccine Project (MVP), established in 2001 with \$70 million in funding from the Gates Foundation with the explicit purpose of developing an affordable conjugate vaccine against serotype A meningitis for use in the Sahel. Proponents of the conjugate vaccine point to both the inefficacy of the current epidemic response strategy and the inability of the polysaccharide to properly confer either herd immunity or immunity in children. As the third argument in the meningitis vaccine debate, this strategy blends the best of both epidemic response and mass immunization strategies by providing a more effective vaccine that would be distributed preventively. By targeting people within an age bracket of 1-29 years who have been shown to be most likely transmitters of meningococcus, the conjugate vaccine induces herd immunity while also preventing meningococcus colonization in youth. Moreover, only one dose is required for people in the age group of 1-29 years (with two doses at 14 weeks and 9 months for children under one year old). Best of all, MVP was committed to providing the vaccine at no more than \$0.50 per dose so it would be easily affordable for African governments. By working with manufacturers in the US, the Netherlands, and India, MVP was able to put together a conjugate vaccine of polysaccharide A along with tetanus toxoid protein, all for only \$0.40 per dose.^{vii}

Is MVP’s conjugate vaccine truly a magic bullet? Phase I trials in India in 2004 and Phase II trials in Gambia and Mali in 2006 have so far proven successful, with the vaccine working safely and effectively. The next round of trials is scheduled to take place with 9 million people in Burkina Faso later this year in preparation for the dry season of 2010. A number of questions about the vaccine, however, are still unclear. When MVP was being launched in 2001, the first wave of W-135 epidemic swept through the belt. Instead of exploring options for including W-135 in its conjugate vaccine, MVP stuck with making monovalent conjugate A vaccine due to its primary interest to making an affordable vaccine that would work well. As F. Marc LaForce, the director of MVP, explained, ““If we could [address] 85% of the burden with the simplest approach, ... to me, that was a completely acceptable wager with public money.”^{xviii} While W-135 continues to be present in the Sahel - and even outside of the Sahel, with a recent W-135 meningitis outbreak in Cameroon - it is usually localized and does not spread



widely (the W-135 in 2000 and 2001 occurred mostly in Burkina Faso and Niger, but not throughout the rest of the belt). If the vaccine trial goes well, MVP hopes that the trial will completely end the bulk of meningitis serogroup A epidemics throughout the Sahel. Though MVP will close soon after the conjugate vaccine's launch, the greater hope is that the expected results from this monovalent vaccine will spur a new project dedicated towards the production of a multivalent vaccine similar to the one currently available in the United States for \$100/dose. Another issue that is becoming less relevant with time as the inauguration of the conjugate vaccine approaches is what to do in the interim.

Though critics of both the epidemic response strategy and mass immunization strategy believe that the future of meningitis treatment lies in conjugate vaccines, some, like Robbins, believe that "immediate implementation of the routine use of group A meningococcal polysaccharide vaccine will be the best way to prepare the public health systems of the meningitis belt for timely acceptance of the conjugate vaccines", and that, most critically, "a great deal of meningococcal disease will be prevented". While this analysis is useful, Robbins' main argument against overzealous conjugate vaccine implementation is that a conjugate vaccine's "cost will be considerably higher than of the polysaccharide alone" and that "all current conjugate vaccines must be administered more than once during the first year of life" – two problems that the MVP has largely solved by creating a cheap vaccine that will only need to be administered once.

If the details behind the mysterious outbreak in Burkina Faso in 2008 are never made entirely clear, the good news is that they may be irrelevant. As a stronger vaccine is made available to the people of Burkina Faso and other countries in the Sahel, the hope is that immunity will be long-lasting and the need for the large-scale operations of the epidemic response strategy will be diminished. The improved efficacy of the conjugate vaccine over the polysaccharide vaccine is largely indisputable: by conferring stronger immunity in a single vaccination at a cheap cost, this is the vaccine the Sahel has been looking for. Though


MVP's serogroup A vaccine cannot truly promise to wipe out meningitis completely until it can also counter the W-135 serogroup, it the most powerful tool yet in the struggle to end the epidemics of the Sahel once and for all.

About the Author:

Aaron Kofman is a recent graduate of Stanford University, where he majored in International Relations and pursued interests in global health and international development. In 2009-10 he is working at the Stanford Medical School on research related to HIV resistance to antiretroviral therapy in Asia and Africa. He is also a project manager for TeachAIDS, a Palo Alto-based nonprofit focusing on global HIV/AIDS education through computer-based educational animations. His future interests lie at the clinical level, where he hopes to work with underserved communities in the US and abroad after obtaining his MD. He can be reached for comments or questions at akofman@stanford.edu.

References

- ⁱ “Burkina Faso: Meningitis death toll now 672.” IRIN News. (1 Apr. 2002.) Online at <http://www.irinnews.org/report.aspx?reportid=30932>.
- ⁱⁱ “Nigeria: Northern states on high alert for meningitis.” IRIN News. (6 Feb. 2009.) Online at <http://www.irinnews.org/Report.aspx?ReportId=82805>.
- ⁱⁱⁱ Rep. UNDP. Online at <http://hdr.undp.org/en/statistics/>. Accessed 9 Mar. 2009.
- ^{iv} Preziosi, Marie-Pierre, F. Marc LaForce, Kader Konde, and Simonetta Viviani. “The Meningitis Vaccine Project.” *Vaccines*. (2007) 25: A97-100.
- ^v Steinhoff, Mark C. “Global Epidemiology of Meningococcal Infections.” Ed. Kenrad E. Nelson and Carolyn M. Williams. *Infectious Disease Epidemiology Theory And Practice*. New York: Jones & Bartlett, 2006.
- ^{vi} “Africa: Fighting meningitis a race against time.” IRINNews. (16 Mar. 2007.) Online at <http://www.irinnews.org/Report.aspx?ReportId=70740>.
- ^{vii} Preziosi, Marie-Pierre, F. Marc LaForce, Kader Konde, and Simonetta Viviani. “The Meningitis Vaccine Project.” *Vaccines*. (2007) 25: A97-100.
- ^{viii} Vermeulen, Marinus, Diederik Van de Beek, and Jan De Gans. “Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis.” *The New England Journal of Medicine* (2004) 351: 1849-859.
- ^{ix} Tinsley, Colin R., Emmanuelle Bille, and Jean-Ralph Zahar. “A chromosomally integrated bacteriophage.” *The Journal of Experimental Medicine* (2005) 201: 1905-913.
- ^x Genton, Blaise, Abraham Hodgson, and Thomas Smith. “Risk factors for meningococcal meningitis in northern Ghana.” *Transactions of the Royal Society of Tropical Medicine and Hygiene* (2001) 95: 477-80.
- ^{xi} Guillaume, Marie. “West African meningitis epidemics driven by the wind.” *Medical News Today* (6 Apr. 2005). Online at <http://www.medicalnewstoday.com/articles/22350.php>, accessed 7 Mar. 2009.
- ^{xii} Molesworth, Anna M., Luis E. Cuevas, Stephen J. Connor, and Madeleine C. Thomson. “Environmental risk and meningitis epidemics in Africa.” *Emerging Infectious Disease* (2003). Online at <http://encyclopedia.com/doc/1G1-109905445.html>, accessed 8 Mar. 2009.
- ^{xiii} Ouedraogo-Traore, R., and Dominique Caugant. “Molecular Characteristics of Neisseria meningitidis Strains Isolated in Burkina Faso in 2001.” *Scandinavian Journal of Infectious Diseases* (2002) 34: 804-07.
- ^{xiv} Taha, Muhamed-Kheir, Isabel Parent du Chatelet, and Jean-Michel Alonso. “Neisseria meningitidis Serogroups W135 and A Were Equally Prevalent among Meningitis Cases Occurring at the End of the 2001 Epidemics in Burkina Faso and Niger.” *Journal of Clinical Microbiology* (2002) 40: 1083-084.

- 
- ^{xv} “Management of People Who Have Received Menomune Meningococcal Vaccine Since 16 May, 2001.” Rep. Public Health Agency of Canada. Online at <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/02vol28/dr2822ea.html>, accessed 9 Mar. 2009.
- ^{xvi} CDC-INFO. “2008 meningitis outbreak [sic].” E-mail to the author. (13 Mar. 2009.)
- ^{xvii} Meningitis Vaccine Project. Online at <http://meningvax.org>, accessed 10 Mar. 2009.
- ^{xviii} Roberts, Leslie. “An Ill Wind, Bringing Meningitis.” *Science* (2008) 320: 1710-715.
- ^{xix} Massenet, Denis, Jermias Inrombe, Dave-Etienne Mevoula, and Pierre Nicolas. “Serogroup W135 Meningococcal Meningitis, Northern Cameroon, 2007.” *Emerging Infectious Diseases* (2009). 15. 8 Mar. 2009.
- ^{xx} Taha, Muhamed-Kheir, Isabel Parent du Chatelet, and Jean-Michel Alonso. “Neisseria meningitidis Serogroups W135 and A Were Equally Prevalent among Meningitis Cases Occurring at the End of the 2001 Epidemics in Burkina Faso and Niger.” *Journal of Clinical Microbiology* 40 (2002): 1083-084. 6 Mar. 2009.
- ^{xxi} Robbins, John B., Rachel Schneerson, and Emil C. Gotschlich. “A rebuttal: epidemic and endemic meningococcal meningitis in sub-Saharan Africa can be prevented now by routine immunization with group A meningococcal capsular polysaccharide vaccine.” *The Pediatric Infectious Disease Journal* 19 (2000): 945-53. 5 Mar. 2009.