Lessons learned from the CDC’s post-exposure prophylaxis program following the anthrax attacks of 2001

The bioterrorism-related outbreak of anthrax in Fall 2001 was the result of unprecedented attacks on residents of the United States. Although addressees of anthrax spore-filled letters were most likely the targets of the attacks, thousands of U.S. postal employees and others were exposed through aerosolization of spores in mail processing facilities. These attacks precipitated decisions to recommend post-exposure prophylaxis (PEP) to an estimated 10,000 individuals potentially exposed to *Bacillus anthracis* to prevent inhalational anthrax.

Initially, the Centers for Disease Control and Prevention (CDC) recommended 60 days of antimicrobial PEP (initial PEP program), mainly either doxycycline or ciprofloxacin. The CDC eventually extended its recommendation to 40 additional days of antimicrobial prophylaxis with or without three doses of anthrax vaccine adsorbed (AVA) under an investigational new drug (IND) protocol (extended PEP program). Overall, approximately 5,420 individuals received education about the extended PEP program. Of these, 1,727 individuals agreed to take antibiotics for a full 100 days, but only 199 also chose to be vaccinated with AVA.

Fifty-seven percent of those who took at least one dose of antimicrobial prophylaxis during the first 60 days of PEP sustained an adverse event (AE), of which less than 1% were considered serious. No deaths were attributed to PEP. Of the thousands of exposed individuals who were advised to take PEP, none developed any form of anthrax, whether or not they elected to take PEP.

Of the 22 diagnosed anthrax cases, 4 (2 cutaneous, 2 inhalational) were suspected to be due to exposure to cross-contaminated mail. Clearly, with thousands of individuals occupationally exposed over several weeks, and potentially millions exposed via cross-contaminated mail, the risk of contracting anthrax was relatively low. Nevertheless, 5 of 11 inhalational cases of anthrax (2 of them postal employees) died and perhaps more would have become ill and died, had PEP not been made available.

Why did so many people not start or complete the initial 60 days of PEP, or choose not to extend their PEP antimicrobial regimen to 100 days and also decide not to receive AVA? Miro and others reported that postal employees chose not to start or complete the initial 60 days for many reasons including fear of or actual side effects, confusion about the efficacy of antibiotics, fear of antibiotic resistance, a belief they did not have a significant exposure, lack of perception of personal susceptibility, and observations that others who were not taking PEP had not become ill.

The reasons for not electing to participate in the extended PEP program described by Martin et al. differ from those who did not participate in the initial PEP program. The two principle reasons for refusing extended PEP were the changes in recommendation in how long to take PEP to prevent anthrax, and the use of an IND protocol, especially as it related to use of AVA. Other reasons included the late timing of offering the initial and extended PEP program to many individuals after presumed first exposure, and the need for informed consent and prolonged follow-up required by the protocol.

Martin’s article describing the extended PEP program makes important contributions to the literature. Both the initial and extended PEP programs provided an opportunity for public health officials to assess the risks of prolonged antibiotic use by thousands of individuals, with or without three doses of AVA. The bad news was that a high percentage of individuals developed one or more AEs with either antibiotic. The good news was that few of the AEs were serious, AVA did not appear to increase the number of AEs, and no one died because of a reaction to antimicrobials or vaccine.

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These findings are similar to an analysis of AEs in a military anthrax vaccination program reported to the Vaccine Adverse Event Reporting System. Together, the studies indicate that PEP can be implemented on a mass scale, AEs related to either antimicrobials alone or with AVA (three doses) are tolerable, and inhalational disease may be prevented. However, it is not possible to conclude that the overall PEP program prevented pulmonary anthrax, as the power to detect a protective effect was probably quite low.

Despite these useful findings, Martin’s descriptive study has several methodologic weaknesses that cast doubts on the generalizability of the findings to other similar situations. First, there were relatively few individuals who enrolled in the extended PEP program and then provided either diary or interview data. In addition, there are no data describing how those who participated in the extended PEP program differed from those who participated only in the initial PEP program, either demographically or in the proportion that sustained AEs.

The accuracy of the data collected through response diaries is also suspect in that at least 44 (2.9%) of the 1528 enrolled in the antibiotic only group reported an AE at the injection site. Also, as the authors state, some participants had AEs that began before their enrollment in the extended program. Although the side effects appeared to be substantially more frequent in the antibiotic and AVA group in the diary data, AEs were substantially fewer in this group in the 2-month follow-up interview, with almost 83% of the group completing the interview. Clearly, self-completed, unverified diary data differ from interview data and must be interpreted cautiously.

What does this study and others examining the PEP program mean for future events requiring mass PEP, at least for anthrax exposure? First, public health officials must be prepared to rapidly implement plans to establish PEP clinics and distribute antimicrobials and/or vaccine to potentially exposed individuals. Fortunately, preparedness efforts were ongoing even prior to the Fall 2001, but accelerated tremendously thereafter with the infusion of substantial federal funding in recognition of the acute need highlighted by this episode.

Even more important to preventing disease is the early detection of the release of anthrax spores that exposes workers or the public. Both the United States Postal Service and the Department of Homeland Security have deployed polymerase chain reaction-based technology to detect potential exposures to anthrax to advance the detection timeline so that the incidence of disease can be reduced or prevented.

Early detection of exposure to anthrax spores should lead to timely prophylaxis as outlined in recent CDC guidelines.

Adherence to PEP recommendations in the initial PEP program varied greatly among the locations where individuals were exposed. This could partly be explained by the demographics of the individuals, the timing between detection of exposure and recommendations for PEP, the apparent confusion on recommendations of what was appropriate PEP, and the changes in recommendations during the entire PEP program. Table 1 in Martin’s report clearly demonstrates vastly different perceptions of the risk-benefit of AVA, very likely due to different recommendations by local officials on the merits of the extended program. There was no assessment of adherence to antimicrobial prophylaxis in the extended PEP program.

Public health officials and others have now reached consensus on the appropriate prophylaxis regimen following anthrax exposure which includes post-exposure use of AVA. Culturally appropriate and timely health education messages and methods promoting adherence, similar to those used in the treatment of latent tuberculosis infection, delivered by trusted individuals, will be needed to ensure greater adherence than that experienced in Fall, 2001 (D. Malwitz, unpublished manuscript, UMDNJ MPH thesis). Eliminating the need for IND protocols would also be helpful to increase adherence, particularly among ethnic and racial groups that are resistant to any treatment that has an experimental halo around it.

During the initial PEP program, public health officials implemented a labor intensive active surveillance program to detect AEs, and this was required during the extended PEP program due to the IND protocol. Given the relative safety of the entire PEP program as determined by Martin’s study and others, active surveillance for AEs is probably unnecessary in a future similar event with exposure of thousands of individuals.

The public health and health care communities hope to never have to respond again to a bioterrorism event. But if it happens, the reports by Martin and others should inform that response, as long as all of us are willing to apply the lessons learned.

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