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ADVANCE: The promises, pitfalls, and future prospects of a European distributed data network for immunization surveillance and research

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Since at least the 1970s, immunization programs have been challenged by periodic vaccine safety scares "going viral" (Kullenkamp 1974, Hall 1999, IOM 2004). The causes of such scares are complex, but likely due in part to the increasing relative prominence of adverse events following immunizations (AEFI) as vaccine coverage increases and the targeted vaccine-preventable diseases decrease (Gangarosa 1998). Being able to answer in a timely manner whether or not a particular vaccine actually causes a specific adverse event became increasingly important. Because the sample size of pre-licensure clinical trials of new vaccines usually number <100,000, detection of rare AEFIs is practical only post-licensure when millions may be immunized. In the United States, the development of a new passive surveillance Vaccine Adverse Event Reporting System (VAERS) in 1990 (Shimabukuro 2015) led to a recognition that while useful for signal generation, more rigorous databases are needed to test hypotheses and answer the causality question. In addition, although pre-licensure trials are usually adequately powered to evaluate vaccine efficacy under highly standardized conditions, evaluation of vaccine effectiveness is often necessary post-licensure to assess the benefits of vaccination in real world settings that may include population groups that were not enrolled in pre-licensure trials (e.g., pregnant women) and that may be subject to other forces, such as waning immunity and herd immunity (Lopalco 2015).

In high income countries, increasing computerization of health care services data, including immunizations and medical visit diagnoses, has allowed the creation of large linked databases to meet the needs for post-licensure monitoring of vaccine safety. Such databases may also provide a relatively inexpensive and rapid method for preliminary estimates of vaccine effectiveness (Lopalco 2015). In the United States, the Centers for Disease Control and Prevention established the Vaccine Safety Datalink (VSD) project (McNeil 2014) and more recently the Food and Drug Administration (FDA) developed the Post-licensure Rapid Immunization Safety Monitoring (PRISM) system (Nguyen 2012). Both systems have

proven valuable in informing U.S. immunization policy. For example, both systems detected a small increased risk of intussusception during post-licensure monitoring of two new rotavirus vaccines (Weintraub 2014, Yih 2014). Post-licensure data, however, have also documented large benefits of rotavirus vaccination in terms of reductions in hospitalizations, ER visits, and deaths from diarrhea (Patel 2011). Thus, policy makers have continued to recommend the current rotavirus vaccines for childhood immunization programs, although the data on the small increased risk of intussusception has been included in the vaccines' package inserts and other educational materials for patients and providers.

In Europe, the UK and Denmark have led the way in the use of large databases for public health surveillance and research. For example, a timely proactive study in the Clinical Practice Research Datalink of chronic fatigue syndrome in adolescent females was key to investigating and refuting the related safety signals in the HPV vaccinated population in the EU (Donegan 2013). The Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium sponsored by the European Centre for Disease Prevention and Control (ECDC) demonstrated the feasibility and advantages of combining data from both UK and Denmark to study a known, rare vaccine risk, measles vaccine-induced thrombocytopenia (Andrews 2012). During the 2009 H1N1 influenza pandemic, a multi-country VAESCO study was conducted to evaluate the risk of Guillain-Barré Syndrome associated with pandemic H1N1 influenza vaccination (Dieleman 2011). The next challenge was to create a sustainable large linked database platform that is pan-European.

This Supplement is devoted to the ADVANCE project, an innovative European effort to develop a framework, through a public-private partnership, for establishing a multi-country distributed database network for vaccine risk-benefit analyses. This large undertaking included engagement of 47 partners across 19 EU countries, with 16 academic or public research institutions, 10 public health organizations (including ECDC), 9 drug regulatory agencies (including the European Medicines Agency), 7 vaccine manufacturers, and other groups. ADVANCE developed critical operating procedures for governance and rules of conduct; obtained administrative approvals; and developed new online tools for data sharing, secure data transmission, data processing and analysis. A distributed data network that allowed primary data to be maintained and processed by the individual database holders with subsequent secure transmission of de-identified local data to a central research data center that consolidated the data from each of the individual providers and performed combined analyses was successfully established. The network was tested in a proof-of-concept retrospective analysis comparing the risk-benefit profiles of whole-cell and acellular pertussis vaccines.

ADVANCE has had a number of successes and accomplishments. It brought together a diverse set of stakeholders, including public health agencies, regulatory authorities, manufacturers and academics. Not to be overlooked is the large number of investigators and other personnel from several European countries that worked collaboratively on the project. Many had not worked in vaccine studies previously, resulting in a new pool of investigators trained and experienced in vaccine study methods. Although it took considerable time and effort, a transparent and trusting working relationship was established and codified in written rules of conduct. Many countries and database holders expressed interest in participating in

the study and a systematic, detailed “fingerprinting” process was undertaken to identify databases that met specific criteria for the proof of concept analyses. A distributed data network was successfully established, including standardized codes for outcomes and vaccines. For the proof-of-concept study, the participating database holders were able to provide data on vaccines administered and safety outcomes, allowing analyses of coverage and safety. Data on benefits (i.e., vaccine effectiveness) proved more challenging and had to be derived from the literature. With these data, a benefit-risk model based on multi-criteria decision analysis (MCDA) was successfully tested.

The completion of the project, however, was not without its challenges. The amount of time and effort to reach agreement on rules of conduct, develop the study protocols, and obtain various administrative approvals took longer than anticipated. A number of countries, even though they had the necessary data, were not able to participate because administrative and other approvals could not be obtained in time. Although the included databases could provide data on vaccine type, manufacturer-specific data were not always available. A common coding nomenclature was not available for vaccines and had to be developed by the investigators. The proof-of-concept was conducted as a retrospective analysis. It will be important to continue to test the system in near-real time or prospectively to have the greatest utility for informing immunization policy and supporting regulatory action. Only the MCDA benefit-risk model was tested; other benefit-risk assessment methods should be considered and evaluated as well.

The ADVANCE project has developed a Blueprint for establishing a European distributed data network for surveillance and research on vaccine coverage, safety, effectiveness, and risk-benefit assessment. Moving forward, continued refinement of the system and long-term support are needed to implement a sustainable system. Further technical developments and refinements would include streamlining the process for establishing working agreements among the various stakeholders and obtaining regulatory and other administrative approvals. Fortunately, the work that ADVANCE has already done in this area should make these processes much smoother and quicker in any future projects, although new data privacy requirements, as in the European General Data Protection Regulation, may have to be addressed. Data improvements, such as availability of vaccine brand and more data on benefits, would make ADVANCE more useful and appealing for regulators, manufacturers and policy makers. Including more countries and databases would make the system more powerful and faster, as well as more likely to have broader public support. Focusing on the capability to conduct rapid signal evaluation and benefit-risk assessments in the same database network should also be important in obtaining more widespread support. It will also be critical to go beyond the initial proof-of-concept study to show that the ADVANCE network can conduct near real time or prospective studies. Such a study is planned and needs to be completed to fully demonstrate how the wealth of available health care data in the EU can be used to generate actionable evidence on vaccine coverage, benefits and risks.

ADVANCE has been funded as a time-limited project through a public-private partnership. Valuable lessons have been learned and the priority now is a sustainability plan that is ready for implementation of the Blueprint. Ideally, ADVANCE will continue as a new, not-for-profit entity and maintain a community and study network, with an infrastructure providing

access to a data-sharing platform, and based on a model which inspires and maintains public confidence via its robust independent scientific outputs. Recognizing the challenges in achieving this ideal should not, however, detract from the importance of ADVANCE's achievements to date. ADVANCE has lived up to its name in moving forward thinking; developing standards, tools and methodologies and bringing together all stakeholders to achieve an EU network ready to address relevant questions in a crucial area of public health.

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