Contagion Without Borders and the Role of International and Comparative Law: The Example of 21st Century Influenza Pandemics

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Societal Benefit of Vaccines

Influenza Vaccines and Regulatory Requirements

Pandemics and Pandemic Influenza Vaccines

Conclusions

Additional Selected Resources
Introduction

Using the example of 21st century global Influenza pandemics, this presentation will explore the thesis that:

- In a global, cross-border industry generally viewed to be beneficial to society and regulated nationally with normally minimal international coordination:
  - there is a direct relationship between the level of international coordination and the probability of success in addressing a global crisis;
  - the legal community can contribute to international coordination and the probability of success by developing support on issues of international and comparative law for the subject-matter experts within the relevant national authorities, international organizations, and industry; and
  - interdisciplinary scholarship is essential for the success of this work of the legal community.
Introduction

• Very briefly, why this subject?
  – I will draw on my experience practicing international and comparative law as an in-house lawyer in the vaccines industry;
  – Although the regulated industry in question here is the vaccines industry, I think many of the same issues with respect to the management of global contagion pertain to other regulated industries;
  – I also think that the lessons that can be learned from reviewing a regulated industry in the extreme situation of a crisis will contribute improvements applicable to less interesting times; and
  – despite my experience in this area, I find there are always unanswered questions and more issues to explore…. 
Legal Issues to be Considered

- National Security/Ordre Public
- Compulsory Licensing
- Compulsory Vaccination
- Regulatory Law
- Quarantine
- Public Policy/Ethics
- Product Approval/Release
- Contracts Law
- Products Liability
- Indemnification
- National Public/Administrative Law
- Conflict of Laws
- Public International Law
Roadmap

• Societal benefit of vaccines:
  – Vaccine-preventable diseases
  – Immunization success in the U.S.
  – Calculating immunization benefits

• Seasonal Influenza vaccines:
  – Licensure and regulatory requirements
  – Manufacture
  – Liability issues and compensation programs

• Pandemics and pandemic Influenza vaccines:
  – Influenza pandemics
  – Pandemic preparedness and regulatory requirements for vaccines
  – Pandemic Influenza vaccine availability
  – Liability issues and compensation programs

• Conclusions
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Vaccine-Preventable Diseases

Fig. 1 Causes of 2.5 million child deaths* out of 10.5 million child deaths globally, 2002
Fig. 1 Causes de décès de 2,5 millions d’enfants* sur les 10,5 millions de décès d’enfants dans le monde, 2002


* Deaths in children aged under 5 years attributed to diseases for which vaccines are currently available. – Décès d’enfants de moins de 5 ans dus à des maladies pour lesquelles des vaccins sont actuellement disponibles.

Source: WHO/IIVB

## Immunization Success in the U. S.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>Maximum Cases Reported</th>
<th>Year Maximum Reported</th>
<th>Reported Cases 2000</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>48,164</td>
<td>1900-1904</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>1921</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271</td>
<td>1934</td>
<td>7,867</td>
<td>94.7%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314</td>
<td>1948</td>
<td>35</td>
<td>97.3%</td>
</tr>
<tr>
<td>Polio</td>
<td>16,316</td>
<td>1952</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>1941</td>
<td>86</td>
<td>100%</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>1968</td>
<td>338</td>
<td>99.8%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>1969</td>
<td>176</td>
<td>99.6%</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>823</td>
<td>1964-1965</td>
<td>9</td>
<td>98.9%</td>
</tr>
<tr>
<td>H. Influenza type b and unknown (&lt;5 years)</td>
<td>20,000</td>
<td>1984</td>
<td>112</td>
<td>99.4%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>26,654</td>
<td>1985</td>
<td>8,036</td>
<td>69.9%</td>
</tr>
</tbody>
</table>

Calculating the Societal Benefits of Vaccines

The Institute of Medicine formed a committee to “develop recommendations to guide federal, state, and congressional decision-making with respect to the purchase of vaccines for the general population, especially underserved groups.”* The committee referred to three types of benefits when considering societal benefits of vaccines as follows:

- “Medical costs that are averted by reducing the incidence of disease
- Nonmonetary benefits, such as years of life and quality of life
- Indirect benefits, such as increased productivity”**

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**Ibid, p. 192.
## Immunization Benefits*

Benefits disease eradication and control by vaccination, in terms of annual life years saved (LYS) and disability-adjusted life years (DALYs) saved

<table>
<thead>
<tr>
<th>Disease</th>
<th>US LYS</th>
<th>US DALY</th>
<th>Africa LYS</th>
<th>Africa DALY</th>
<th>Global LYS</th>
<th>Global DALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox(^a)</td>
<td>1,685,740</td>
<td>NA</td>
<td>933,065</td>
<td>NA</td>
<td>5,000,000</td>
<td>NA</td>
</tr>
<tr>
<td>Polio(^b)</td>
<td>212,690</td>
<td>NA</td>
<td>484,230</td>
<td>279,000</td>
<td>35,750,000</td>
<td>1,725,000</td>
</tr>
<tr>
<td>Measles(^c)</td>
<td>5,811,852</td>
<td>26</td>
<td>2,125,500</td>
<td>17,463,000</td>
<td>71,500,000</td>
<td>29,838,000</td>
</tr>
<tr>
<td>Tetanus(^d)</td>
<td>42,705</td>
<td>9</td>
<td>2,801,500</td>
<td>3,039,000</td>
<td>56,030,000</td>
<td>12,020,000</td>
</tr>
</tbody>
</table>

NA: not available.


\(^b\) Dr. Matthew McKenna at CDC; Murray and Lopez, Global Burden of Disease, 1999; Children’s Vaccine Initiative, World Health Organization, 1995 Note: estimate of US life years saved is based on 21,269—average number of paralytic polio cases times an assumed 50% mortality rate between 1951–1954 times an assumed 20-year life expectancy (source: MMWR, 2 April 1999). Estimate of African life years saved is based on difference between 1999 polio cases (http://www.policeradication.org/pdfs/polio_news_no7.pdf, Page 3) and 1988 cases (http://www.ifrc.org/what/health/archiv/fact/fpolerad.htm) of 35,000–2718 times assumed 15-year life expectancy.


Introduction

Societal Benefit of Vaccines

**Influenza Vaccines and Regulatory Requirements**

Pandemics and Pandemic Influenza Vaccines

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Influenza Vaccines

- Influenza vaccines contain components of the virus, sometimes along with an adjuvant, to stimulate the body’s immune response to create protective antibodies against the disease.

- This is a biological product, therefore, development and manufacture are generally more challenging than for a chemical pharmaceutical product.
  - Virus is grown first in eggs.
  - Biological process is not always predictable.
  - Sterile manufacturing environment is required.

- Typically three strains in the annual Influenza vaccine (trivalent vaccine).
  - Two A strains.
  - One B strain.

- Vaccine strain composition changes each year to match then current virus mutations, hence “seasonal” Influenza vaccine.

- Virus surface proteins hemagglutinin (16 subtypes) and neuraminidase (9 subtypes) are virus identifiers (i.e., H1N1)*

- CDC and WHO identify the Influenza strains circulating, and FDA and WHO instruct manufacturers which strains to include in the seasonal vaccine.

Influenza Vaccine Licensure and Regulation

John Wood from NIBSC (National Institute for Biological Standards and Control, UK) and Roland Levandowski from CBER (Center for Biologics Evaluation and Research, U.S.A.) have summarized their key message with respect to the influenza vaccine licensing process as follows:

“Annual registration of influenza vaccines is a complicated process that is governed by:

– Severe time constraints;
– Frequent and unpredictable changes in one or more of the vaccine virus subtypes;
– Different registration requirements by different national and international regulatory authorities.”*

Influenza Vaccines/Regulatory Timeline*

The full process, in a best case scenario, can be completed in five to six months. Then the first final pandemic vaccine lot would be available for distribution and use.

**Activity**

**At WHO Collaborating Centres**
- Identification of new virus
- Preparation of the vaccine strain
- Verification of vaccine strain
- Preparation of reagents to test vaccine

**At Manufacturer**
- Optimization of virus growth conditions
- Manufacture of bulk vaccine
- Quality control
- Vaccine filling and release
- Clinical trial (in certain countries)

**At Regulatory agency**
- Review and release

**Key:** The arrows with dotted lines preceded by non-broken arrows indicate the time period required for the first time an activity is done (non-broken arrow line) that is then repeated (dotted arrow line). The solid lines signify that the activity takes place within a finite period.

Influenza Vaccines/Antigenic Drift*

Influenza Vaccine Virus Selection

Influenza Vaccine Manufacturers for U.S. and Europe with the location of the manufacturing facility:
- Baxter: Austria, Czech Republic
- CSL: Australia
- GSK Bio: Belgium
- GSK/ID Biomedical: Canada
- Medimmune: U.S.
- Novartis Vaccines and Diagnostics: Germany, UK, Italy
- sanofi pasteur: U.S., France
- Solvay: Netherlands

Influenza vaccine manufacturing facility must have a local manufacturing license from the authorities in the country of the location of the facility

Influenza vaccine product must be approved for sale in the country where it will be sold

Manufacturing capacity is finite

Only facilities used for seasonal Influenza vaccine manufacture can be used for pandemic Influenza vaccine manufacture, although not all facilities which produce seasonal Influenza vaccine produce pandemic Influenza vaccine
## Vaccine Regulatory Requirements

<table>
<thead>
<tr>
<th>U.S.A.</th>
<th>EU, Example of UK</th>
</tr>
</thead>
</table>
| • Vaccines are subject to Federal Food, Drug, Cosmetic Act and Public Health Service Act.  
  • CBER (Center for Biologics Evaluation and Research) at FDA has primary responsibility. | • Vaccines are regulated by the UK Licensing Authority, statutory body of health ministers, and the MHRA (Medicines and Healthcare products Regulatory Agency).  
  • NIBSC (National Institute for Biological Standards and Control) is the primary UK biologics agency. |
| • Vaccines must have approved BLA (biologics license application) covering manufacturing process, safety, effectiveness and including FDA batch release requirement. | • Vaccine must have marketing authorization for sale in EU member states covering quality, safety, efficacy, and requiring government batch release.  
  • With EU Mutual Recognition Procedure, UK as Reference Member State, but other member states review and may object.  
  • Newer centralized procedure co-ordinated by EMEA (European Medicines Agency) applies to pandemic Influenza vaccines. |
| • Vaccine must be manufactured in compliance with U.S. cGMP (current good manufacturing practice).  
  • FDA inspects for compliance with cGMP and BLA manufacturing provisions. | • Vaccine must be manufactured in licensed establishments complying with EC cGMP, with a Qualified Person issuing a certificate for each batch.  
  • The MHRA inspects for compliance. |
Harmonization of Vaccines Regulation

• Technical Issues
  – ICH Guidelines (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use): EU, Switzerland, Japan, U.S., Canada coordination by regulatory authorities and industry of matters pertaining to quality, safety, efficacy, and multidisciplinary technical issues*

• Product Licensure
  – EU harmonization: Rules Governing Medicinal Products in the EU**
  – U.S.-EU Clinical Initiative: Pilot phase begun on September 1, 2009 of a bilateral GCP (Good Clinical Practices) initiative between the FDA and EMEA (European Medicines Agency) to conduct information sharing on inspections and developments in GCP-related regulatory and legislative matters and to collaborate on GCP inspections***

• Regulatory Matters
  – February 14, 2005, FDA and MHRA signed information sharing agreement with respect to one manufacturer during Influenza vaccine supply emergency****
  – September 2005, FDA, EMEA, and European Commission Enterprise and Industry Directorate-General extend confidentiality arrangement*****

** See http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm
***Announced by both FDA and EMEA on August 3, 2009. See, for example, FDA press release at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm174983.htm.
****See www.fda.gov/NewsEvents/Testimony/ucm161669.htm.
Vaccine Liability Issues

• Vaccines are intended to prevent rather than treat disease and to protect large numbers of people, thus the careful risk benefit analysis during the approval process and the stringent regulatory regime for clinical trials and for manufacturing

• It is known that some persons will suffer adverse events soon after vaccines are administered, and the PI (prescribing information) which accompanies the product provides known information about adverse events and contraindications

• Unrelated health events may occur coincidentally with or close in time to vaccination: if large numbers of people are vaccinated, such events are statistically likely to occur

• Causal relationship is often hard to establish

• Then where does liability belong?
  - With the manufacturer who manufactured according to cGMP and as approved by the regulator?
  - With the government which approved the vaccine and encouraged or perhaps required vaccination?
  - With the employer who required vaccination?
  - With the administering physician or nurse?
Vaccine Injury Compensation Programs

• Remedies available for vaccine injury vary from country to country
• Many countries have vaccine injury compensation programs founded on a cost-effectiveness analysis with respect to the societal benefit of vaccines
• A 1999 survey* of 13 programs showed numerous variations, including, relating to:
  - Administrative entity: federal; state; semi- or non-governmental
  - Vaccines covered: compulsory; recommended; all administered; governmentally provided; all approved products; childhood
  - Compensable vaccine-related injuries: all; disability or death; rare and severe; beyond the usual; as set out on a table
  - Proof needed: clear and convincing evidence; reasonable probability; balance of probabilities; unspecified
  - Elements of compensation: medical costs; disability pension; death benefits; funeral costs; non-economic damages; lump sum payment; attorneys’ fees
  - Source of funding: federal; state; mix of federal, state, and local; employers, employees, auto licensing fees; manufacturers alone or together with federal, state and/or local contributions
  - Appeal and litigation rights

Available Remedies in U.S. for Seasonal Influenza Vaccine

• Vaccine Injury Compensation Program (VICP)*
  - Applies to 16 vaccines listed in injury table, including seasonal Influenza vaccine
  - Funded by excise tax on vaccine
  - No-fault compensation system according to table

• Consider also Restatement (Second) of Torts, Section 402A, comment k re unavoidably unsafe products as being neither defective nor unreasonably dangerous if properly prepared and accompanied by proper directions and warning**

• Current issues***:
  - more than 5,000 consolidated cases alleging link between vaccines and autism (see www.hrsa.gov/vaccinecompensation)
  - federal preemption of state law under challenge
  - effect of Restatement (Third) of Torts


Available Remedies for Seasonal Influenza Vaccine in EU, Germany and France as Examples

- European Directive 85/374/EEC on defective products has been implemented, but vaccine injury compensation programs vary throughout the EU*

- Germany relies on the Infektionsschutzgesetz, IfSG, Gesetz zur Verhütung und Bekämpfung von Infektionskrankheiten beim Menschen (§§60, 61) (prior to January 1, 2001, BSeuchG, Bundesseuchengesetz); and Bundesversorgungsgesetz, BVG (§89)**
  - Coverage for harm beyond the usual from recommended or required vaccines, including seasonal Influenza vaccine
  - Compensation for medical costs, disability pension, funeral costs
  - Current issue: burden of proof, but few cases in the courts

- France in 2002 created ONIAM (Office National d’Indemnisation des Accidents Médicaux)***
  - Coverage for harm from required vaccines
  - Compensation for a wide range of temporary and permanent harm to be determined on a case by case basis within a set range
  - Current issue: allegations that Hepatitis B vaccinations in the 1980’s caused multiple sclerosis, with many cases in the courts

*Although not addressing vaccines specifically, see generally, Duncan Fairgrieve, Editor, Product Liability in Comparative Perspective, Cambridge: Cambridge University Press, 2005.

**Available online at www.juris.de.

***See http://www.oniam.fr/vaccinations.
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Emergence of an Influenza Pandemic

THREE CONDITIONS

1. A new Influenza virus emerges (antigenic shift)
2. The virus infects humans
3. The virus spreads efficiently and in a sustained manner from human to human

The number of infections may be limited by pre-planned control measures, including antiviral medications, but the key question remains…

How fast can the population be vaccinated and protected?
Influenza Vaccines/
Antigenic Shift*

*Source: National Institute of Allergy and Infectious Diseases (NIAID):
Influenza Pandemics Historically

Pandemic Preparedness

In the 2009 revision of the phase descriptions, WHO has retained the use of a six-phased approach for easy incorporation of new recommendations and approaches into existing national preparedness and response plans. The grouping and description of pandemic phases have been revised to make them easier to understand, more precise, and based upon observable phenomena. Phases 1–3 correlate with preparedness, including capacity development and response planning activities, while Phases 4–6 clearly signal the need for response and mitigation efforts. Furthermore, periods after the first pandemic wave are elaborated to facilitate post pandemic recovery activities.

The current WHO phase of pandemic alert is 6.

Pandemic Preparedness

- **Pandemic Preparedness Plans** - Generally agree to take guidance from WHO, establish prioritization of individuals to be vaccinated, explain relevant emergency procedures

- **Pandemic Influenza Vaccine Regulatory Process**
  - U.S.: Strain change approval process [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm);

- **Purchase of Pandemic Influenza Vaccine**
  - Primarily bilateral contracts between national governmental entities and individual vaccine manufacturers, some dating back to 2005/2006, others more recent
  - Donations: September 18, 2009 announcement that the US, Australia, Brazil, France, Italy, New Zealand, Norway, Switzerland, and the UK will donate ~10% of their vaccine to less-developed nations follows previous announcement that certain manufacturers will donate vaccine to WHO*

Pandemic Influenza Vaccine Availability

1. Individual:
   - Vaccine Available
   - Vaccine Not Available

2. National/Local Authority:
   - Contracted for Vaccine Supply?
     - Yes
       - For whole population
       - Priority
       - Distribution Logistics in Place?
         - Yes
           - Assuming vaccine ordered, can it be GMP produced?
             - Yes
               - Quantities available?
                 - Sufficient
               - Insufficient
             - No
         - No
   - No

3. Manufacturer:
   - Assuming vaccine ordered, can it be GMP produced?
     - Yes
       - Quantities available?
         - Sufficient
         - Insufficient
     - No

4. WHO:
   - Surveillance/Declaration of Influenza Pandemic
Pandemic Influenza Vaccine Availability

1. Individual:  
   - Vaccine Available
   - Vaccine Not Available

2. National/Local Authority:  
   - Contracted for Vaccine Supply?
     - Yes
     - No
     - For whole population
     - For portion of population
     - Priority
     - No priority

3. Manufacturer:  
   - Distribution Logistics in Place?
     - Yes
     - No
     - Assuming vaccine ordered, can it be GMP produced?
     - Yes
     - No
     - Quantities available?
       - Sufficient
       - Insufficient

4. WHO:  
   - Surveillance/Declaration of Influenza Pandemic

Then what?  
- Antivirals?
- Quarantine?
- Wrongful Death Suits for Failure to Supply?
- School Closures?
- Border Closures?
- Breach of Contract?

Why?
- Delay?
- Supply Issue?
- Mfg Issue?
- Biologics Issue?
- Force Majeure?
Available Remedies in the U.S./Pandemic Influenza Vaccine

- VICP (Vaccine Injury Compensation Program) does not apply
- PREP Act (Public Readiness and Emergency Preparedness Act)* created a specific compensation scheme as was done for Swine Flu in 1976 and Smallpox in 2003**
  - Subject to Declaration by Secretary of Health and Human Services (HHS) recommending “Covered Countermeasure” for a public health emergency***
  - Persons alleging injury must seek compensation from the federal government
  - Federal government has right to sue manufacturers for specified misconduct
  - No-fault compensation system according to table of covered injuries established by the HHS Secretary

Available Remedies for Pandemic Influenza Vaccine in EU, Germany and France as Examples

- **Germany:** STIKO (Die Ständige Impfkommission) of the Robert Koch Institut has recommended vaccination against the H1N1 Influenza virus,* paving the way for the same remedies as for seasonal Influenza vaccine.

- **France:** Pandemic Influenza vaccine should be subject to same coverage through ONIAM as seasonal Influenza vaccine**

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**See “Plan gouvernemental de prévention et de lutte ‘Pandémie grippale’”, Office of the Prime Minister, February 14, 2006, Section C6(1.6),
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I concur with the statement by David Fidler and Martin Cetron that:

“Not only is international law becoming more important in thinking about public health in the United States, but also globalization generally is affecting how U.S. public health will evolve in coming decades. We call for public health lawyers, international legal practitioners and academics, and other experts to increase attention in their respective activities on the international and comparative features of U.S. public health and the law that serves the public health.”*

Conclusions

• Furthermore, I encourage the lawyers, academics, and experts to work together to form centers of excellence to provide the support needed in emergencies and the innovation required in this era of globalization; and

• I believe that this challenge goes beyond the field of public health to other regulated industries.
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• Influenza Pandemics

• Public Health