

## Vaccine Development & the BWC

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In preparation for the forthcoming Seventh Review Conference of the Biological and Toxin Weapons Convention (BWC), the Harvard Sussex Program has produced a series of papers considering developments in science and technology of relevance to the Convention. This paper assesses developments in science and technology related to vaccine technology.

### Understanding vaccine technology

The basic principles of vaccine action are the same for all types of vaccines: exposure to a particular pathogen (bacterial, parasitical, viral and some toxins) or part thereof sensitises the immune system to generate an immune response which enables the body to fight the pathogen more effectively upon re-infection.

The process of developing vaccines is complex, time consuming and costly. Vaccines require progression through a number of stages which the World Health Organisation has characterised as “discovery, process engineering, toxicology and animal studies to human Phase I, II and III trials.”<sup>1</sup> For some diseases, the development process may take up over a decade and estimated R&D costs can go as high as \$1 billion.<sup>2</sup> Investing large sums of money, however, is no guarantee of success, as new vaccines do not necessarily emerge. Some vaccines have eluded discovery for over a century.<sup>3</sup>

Figure 1 (overleaf) illustrates the three generations of vaccines which are now available. First generation vaccines require disease agents to be grown or cultivated. The agent is then administered, either in weakened or inert form, to stimulate an immune response. Vaccines of this kind have been used to effectively control (or eradicate) a number of diseases.<sup>4</sup> Advances in

*Vaccine technology has progressed considerably with increased understandings about immunology, advances in vaccine production processes and new modes of delivery.*

*Research activity related to vaccines is dynamic, globally distributed and marked by international collaboration*

*Vaccine development has implications for Articles I, III, IV, VII and X*

immunology and molecular biology have enabled the production of second and most recently third generation vaccines. Second generation vaccines use only the specific part(s) of the pathogen (the antigen).<sup>5</sup> Third generation vaccines are still in the experimental phase. The most recent addition in vaccinology is the DNA vaccine in which either ‘naked DNA’ is used directly, or packaged in a recombinant virus or bacteria. Thus far four DNA vaccine products have been licensed.<sup>6</sup>

### Vaccine identification and effectiveness

Drug discovery and vaccine development has experienced a renaissance over the last two decades.<sup>7</sup> Genomic and proteomic approaches have enabled novel vaccine approaches. Drug identification has benefitted from increased speed and decreased costs by the wide-spread use of high-throughput screening (HTS). HTS is the automated screening of large chemical libraries for activity against biological targets. Introduced in the mid 1990s, HTS has been optimised and screening capacity has steadily increased

1 World Health Organisation (2006) “Development of new vaccines”, Fact Sheet no 289, Revised December 2006.

2 EFPIA The Pharmaceutical Industry in Figures 2009 (revised)

3 IAVI (2008) “Aids Vaccine Blueprint 2008: A Challenge to the Field, a Roadmap for Progress” International AIDS Vaccine Initiative

4 This also includes vaccines derived from related agents for example the vaccinia vaccine used to eradicate smallpox.

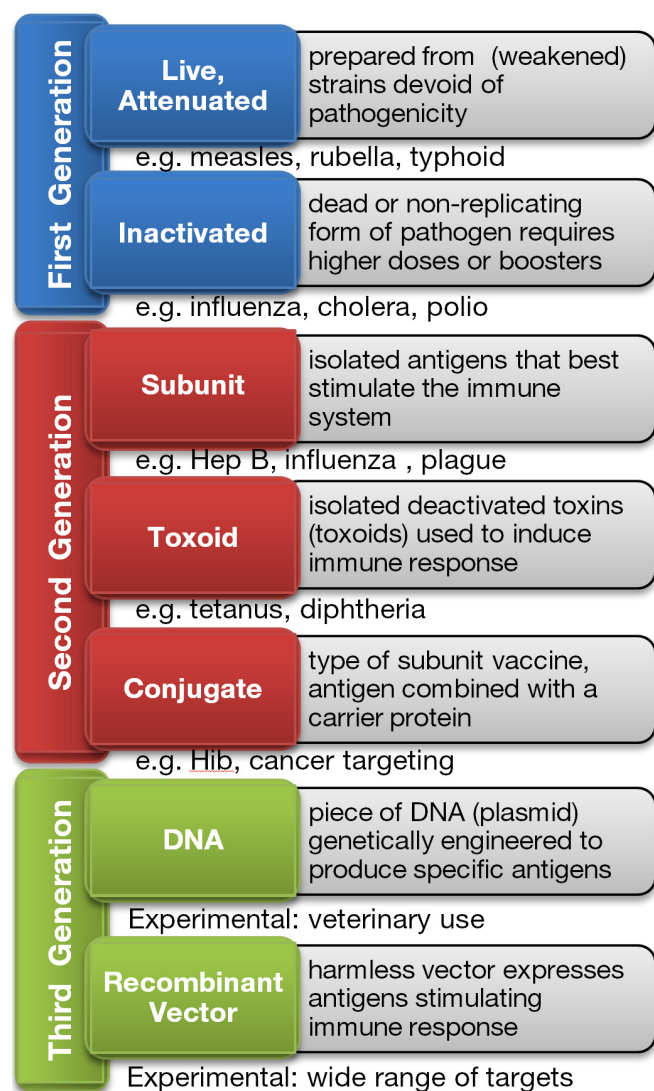
5 An antigen is a substance which, when introduced into a living organism, stimulates the production of an antibody: ‘antibody generator’

6 Liu, M (2011) “DNA vaccines: an historical perspective and view to the future”, *Immunological Reviews*, 239(1), 62-84.

7 Serruto, D. and R. Rappuoli (2006). “Post-genomic vaccine development.” *FEBS Letters*, 580(12), 2985-2992.

(hundreds or thousands of chemicals simultaneously).<sup>8</sup>

**Figure 1: Vaccine types**



A more general shift in pharmaceutical research from *in vivo* (in an organism), to *in vitro* (in a test tube), to *in silico* (in the computer) is benefitting vaccine research and development. The use of computational techniques (e.g. bio-informatics), have allowed what has been called a 'rational design' approach. This shift has reduced or removed the need to cultivate pathogens as well as reduced timeframes of vaccine candidate identification and provided routes to vaccines which have hitherto been difficult to develop.

Vaccine technology has also advanced in the identification of substances used to raise a vaccine's potency. These substances, called adjuvants, have little or no antigenic effect themselves but boost the efficacy of vaccines so that the doses required for immunization can be lowered and thus stretch vaccine supplies.

Despite numerous advances, and a global research effort, the intricacies of host pathogen interactions still render a number of vaccine targets elusive.

## Vaccine Production

The ability of biological agents to rapidly mutate and develop resistance to stockpiled vaccines necessitates a responsive vaccine production capability. The need for rapid production was again shown when concerns were raised about the capability of traditional production methods to generate sufficient amounts of vaccines during the influenza pandemic (H1N1) in 2009. Various technologies – biotechnological and chemical – are applicable to vaccine production. Whereas first generation vaccines rely on the cultivation of the disease-causing agent, second and third generation vaccines (see Figure 1) can be produced with more reliable biotechnological processes. This is of particular interest where the cultivation or attenuation of the pathogen is difficult, or dangerous.

The line between biology and chemistry is blurred in this area with the production of "organic chemicals with biotechnological processes and [the synthesis of] biological molecules by chemical means".<sup>9</sup> This convergence allows a variety of vaccine production methods, including:

- cell cultures and cell suspension bioreactors
- recombinant DNA, metabolic engineering and synthetic biology (i.e. manipulate or create organisms to produce compounds)
- (total) chemical synthesis (peptide synthesis, e.g. toxoid vaccine production)
- transgenic animals or plants (expressing compounds in milk or plant tissues)

However, traditional approaches still prevail and production processes have benefitted from streamlining and process innovation. These developments have enabled rapid production of components for vaccines, increased yields, and allowed a shift from large scale production processes to smaller scale operations.

<sup>8</sup> Mayr, L & Fuerst, P (2008) "The future of high-throughput screening", *Journal of Biomolecular Screening*, 13(6), 443-8.

<sup>9</sup> Tucker, J (2010) "The convergence of biology and chemistry: Implications for arms control verification", *Bulletin of the Atomic Scientist*, 66(6), 56-66.

**Figure 2: Global distribution and patterns of collaborations of publications on vaccine development. (Source: ISI Web of Science)**



## Delivery of Vaccines

Vaccines can be administered by a number of routes: via hypodermic needle, ingestion, topical application (e.g. creams), gene guns, oral and nasal spray, or inhaled as aerosols. Significant advances have occurred in the delivery of drugs and vaccines. This is partly driven by a need for safe, non-invasive and efficacious means for mass vaccination campaigns where stable, needle-free vaccine delivery systems are of particular interest. In order to enable this development a number of technological platforms have been exploited, including microencapsulation and nanotechnological approaches.<sup>10</sup>

For DNA vaccines,<sup>11</sup> research is also looking towards virus and bacteria facilitated gene delivery of DNA vaccines, which involves the construction and delivery of recombinant viruses or bacteria which produce antigens inside the body to stimulate an immune response.

<sup>10</sup> Bachmann, M & Jennings, G (2010) "Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns", *Nature Reviews Immunology*, 10(11), 787-796

<sup>11</sup> Whereas the traditional vaccines use antigens directly to elicit the desired immune response, DNA vaccines are based on the DNA which codes for the antigen, which is then produced inside the body.

## Global nature of vaccine research

Figure 2 above illustrates the global distribution of vaccine research. The shaded areas represent countries where papers have been authored over the last decade, instances of authorship during the period 2006-2010 are represented by nodes – the size of which is proportional to the number of instances – and international co-authorship is shown by the grey connecting lines.<sup>12</sup>

It is possible to discern three clusters of activity on this map: North America, Europe and South East Asia. These clusters are also prominent in a global trend analysis of industrial R&D activity. Although major vaccine manufacture is global, about two-thirds of the vaccine industry's research and development activities are based in Europe. Outside of North American and Europe the most prominent regions of vaccine production capacity include South East Asia, China and Brazil. Whilst illustrating vaccine publications in peer-reviewed journals, Figure 2 also appears to correlate with clusters of industrial research and development activity.

<sup>12</sup> Data is sourced from ISI Web of Science, which covers over 10,000 high-impact journals in the sciences, social sciences, and arts and humanities, from 76 countries.



## Relevance to the BWC

Article I	Article I covers all agents regardless of “origin or method of production” without a prophylactic, protective or other peaceful purpose, as well as all means “means of delivery”. Accordingly, the hostile application of advances related to vaccine development is explicitly prohibited under the BWC. Novel production routes, such as transgenic plants or chemical means of production, as well as novel delivery methods thus require adequate regulation.
Article III	International trade in equipment and material used in vaccine development, production and delivery may require vigilance in regard to their use and purpose. Advances in production techniques mean that even small scale equipment is capable of producing high-yields. However, export control related measures for vaccine development need to be proportional to avoid hampering legitimate activities.
Article IV	Legislation to prevent the development, production, of agents, toxins, equipment as well as means of delivery, requires a delicate balance to be struck so as to not hamper vaccine research and development whilst ensuring that the provisions of the Convention are fulfilled.
Article VII	The provision of assistance and support to mitigate or limit danger resulting from violations of the Convention may require the mobilisation of vaccine production capacities. This may become more pertinent with shifts to flexible and responsive production capabilities and a foreseeable shortening of vaccine development timeframes.
Article X	Article X refers to co-operation in the “prevention of disease”. There is a high degree of international collaboration, as illustrated in Figure 2. Two aspects of vaccine technology may bear strongly on Article X: sharing of pathogen samples to develop vaccines; and the sharing of vaccines against pathogens. Both, pathogen ownership on grounds of territorial origin, and conversely withholding of vaccines on grounds of, for example, intellectual property rights, maybe opposed to the notion of co-operation embodied in Article X.

Scientific and technological advances in vaccine development and production are intricately linked to the BWC. The dual use nature of the technology and many of the developments – particularly developments in delivery – continue to

have implications for the BWC, but particularly Articles I, III, IV, VII and X.

Changes in vaccine production techniques may make the production of vaccines more agile and responsive with great societal benefits, but it may also mean that capacities for nefarious purposes may be mobilised more rapidly.

## Recommendations

The ability to rapidly identify vaccine candidates and develop, produce, target and deliver medical countermeasures to respond to outbreaks of disease – regardless of origin – serves to reinforce the Convention by minimising the strategic utility of biological weapons. Progress in vaccine production technologies can be seen as strengthening the BWC, as well as providing public health benefits.

Yet, at the same time, developments in the science and technology associated with vaccine production and delivery remain vulnerable to hostile exploitation. Advances in vaccine delivery techniques, may be one area States Parties may wish to monitor closely over the coming decades.

Vaccine technology is one area in which technological convergence with chemistry is most evident. States Parties may wish to consider their relationship with the Chemical Weapons Convention’s implementing body, particularly with its Scientific Advisory Board.

Any effective action intended to impose greater controls on vaccine delivery must be proportional and take into consideration both the vast benefits derived from improvements in the efficiency of drug delivery and a range of other activities being conducted outside the BWC.

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*For more information about the project visit <http://hsp.sussex.ac.uk/sandtreviews/>*

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