



The vaccine gap between Japan and the UK

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ABSTRACT

Objective: To study and compare the Japanese vaccine policy with the policy in the UK and to discuss factors that may explain the gap in vaccine availability between the two countries. **Methods:** We analysed approval and immunisation programme data from Japan and the UK for 20 common vaccines, all of which were approved and available from the UK National Health Service.

Results: Of these 20 common vaccines, only four were introduced in Japan. Of the 16 unapproved vaccines, 11 were combination vaccines. Indications for the other five unapproved vaccines were the prevention of infection with meningococcus (3 vaccines) and pneumococcus (2 vaccines). Coverage of diphtheria, tetanus, pertussis, and poliomyelitis vaccines was similar between the two countries whereas that of measles and rubella was higher in Japan.

Conclusions: These results show that there is still a large gap between Japan and the UK regarding access to 20 common vaccines and immunisation programmes. The keys to closing this gap include: (1) revision of vaccine regulations, (2) amendment of vaccine-related laws to secure funding and cooperation between professionals and public health authorities, and (3) improvement in the perception of vaccines among the general public and mass media.

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1. Introduction

Although many health-related indicators, such as life expectancy and the infant mortality rate show that the health situation in Japan is among the best in the world [1], there is a large gap between Japan and other developed countries in the use of vaccines to prevent serious infections [2]. For example, the 7-valent pneumococcal conjugate vaccine (PCV) was only recently approved in Japan (October 2009), more than 8 years after its approval in the UK. Many common vaccines, including those for measles, mumps, and rubella (MMR), the inactivated

poliovirus vaccine, and combination vaccines, are not yet available in Japan. This vaccine gap has major implications for public health both in Japan and in other countries. From the perspective of global public health, Japan is cited as an exporter of infectious diseases to countries that have those diseases under better control through vaccination [3]. Global interconnectedness allows infectious diseases to spread greater distances than ever before.

In the case of meningococcal vaccines, the epidemiology of meningococcal meningitis, which has an incidence of around 1000 cases per year in England and Wales [4], but only around 10–20 cases per year in Japan [5], can explain the vaccine availability gap. In other cases, however, the characteristics and causes of the vaccine gap are multifactorial. A large gap between Japan and other developed countries still exists regarding access to new drugs [6,7], despite several important reforms in the Japanese drug approval system. These included the implementation of the International Conference on Harmonisation of

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Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice, the establishment of a new regulatory authority in 1997, and the implementation of Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5) guidelines in 1998 [8,9]. Apart from vaccine development and regulation, one possible cause for the gap relates to the organisation and funding of the immunisation programme [10]. In Japan, the immunisation programme is outside the national health insurance system, whereas in the UK, the immunisation programme is an important part of the NHS. Funding of the immunisation programme in Japan [11,12] has historically been determined by local governments, with the effect of subsidies being sometimes questionable [13]. The effect of public perception on vaccine use is another common problem in developed countries. This is exemplified by the low MMR vaccine coverage in the UK following negative publicity about possible links between the vaccine and autism [14]. The outbreak of pertussis in several US states was probably caused by perception-related vaccine refusal [15].

The purpose of this study was to identify factors contributing to the vaccine gap between Japan and the UK and to advocate solutions for overcoming the problem. We compared data from the vaccine approval and immunisation programmes of the two countries. We selected the UK as a comparator because Japan and the UK have the following background features in common. First, the UK, like Japan, provides a National Health Service. Second, both the UK and Japan offer a non-compulsory immunisation programme. Third, according to ICH guidelines [16], the regulation of vaccines is harmonised between Japan and the EU, of which the UK is a member state. Fourth, both the UK [14] and Japan [17] suffered the effects of negative public perception and widespread concern regarding the MMR vaccine. These similarities highlight the vaccine gap and allow us to analyse its causes.

2. Methods

2.1. Study design

Cross-sectional study of documents published on regulatory agencies' websites.

2.2. Data sources

To compare the approval status of vaccines in Japan with that in the UK, we analysed data on 20 common vaccines routinely offered to children or available from the NHS to adults in certain 'at risk' groups. The 20 common vaccines are all approved in the UK and listed in the electronic Medicines Compendium (eMC) [18] and European public assessment reports (EPAR) [19]. European legislation aims to ensure that the terms by which vaccines are authorised are harmonised across the EU. The European Medicines Agency takes responsibility for the authorisation of vaccines, working with national medicines regulatory authorities, such as the Medicines and Healthcare products Regulatory Agency in the UK.

Japanese approval data were obtained from the Pharmaceuticals and Medical Devices Agency (PMDA) website

in the new drug approval section [20], which included a review of all new molecular entities and biologics approved in Japan between June 1999 and March 2012. The UK approval (market authorisation) data were obtained from the eMC [18]. A more detailed description of the regulatory review of the vaccines is given in EPAR [19]. The Japanese immunisation data were obtained from the Infectious Disease Surveillance Center [21]. The UK immunisation data were obtained from the NHS Information Centre website [22].

2.3. Evaluation and analysis

Documents were examined for administrative information and the dates and types of regulatory approval were recorded. Approval delay was defined as the difference between the date of approval in Japan and that of first authorisation in the UK. Review time was defined as the time between the date of application for approval and the actual date of approval. Because of the limited number of vaccines analysed, results are presented in a descriptive manner without statistical interpretation.

3. Results

Table 1 shows approval status data for 20 common vaccines. Four vaccines, i.e., *Haemophilus influenzae* type b (Hib), bivalent and quadrivalent human papillomavirus (HPV), and 7-valent PCV, were introduced in Japan 173, 25, 57, and 104 months later, respectively, than in the UK, whereas the review times for bivalent and quadrivalent HPV, and 7-valent PCV were longer by only 7, 2, and 9 months, respectively, than those in the UK. Although the review time for the *Haemophilus b* conjugate vaccine was 46 months, this is still much shorter than the launch delay which was 173 months. Of the 16 unapproved vaccines in Japan, 11 were combination vaccines. Indications of the five other unapproved vaccines were for the prevention of infection with meningococcus (3 vaccines) and pneumococcus (2 vaccines).

Table 2 shows the recommendations for and coverage of the vaccines. Hib, PCV, mumps, and HPV vaccines, which are recommended in the UK, are all voluntary in Japan. Meningococcal vaccines are not available in Japan. The coverage of diphtheria, tetanus and pertussis (DTP), and poliomyelitis vaccines was similar between Japan and the UK. That of measles and rubella was higher in Japan. No official coverage data were available for voluntary immunisation in Japan, i.e., for Hib, PCV, and mumps.

4. Discussion

Our study confirmed and characterised the vaccine gap between Japan and the UK. Two of the 4 vaccines that were approved by both countries were approved in Japan 173 and 104 months after their approval in the UK, with a review time of 46 and 25 months, respectively. Although we could not precisely identify the development time, the review time cannot explain the launch delay of these vaccines. Most of the delay is presumably due to delays in

Table 1Approval data on 20 common vaccines in Japan and the UK.^a

Generic name	Proprietary name	Approval application (Japan)	Date of approval		Approval delay ^{b,c}	Review time ^{b,d}	
			Japan	UK		Japan	UK
Diphtheria, tetanus and poliomyelitis	Revaxis	NA	UA	Jun-03			
Diphtheria, tetanus, pertussis and poliomyelitis	Repevax	NA	UA	Nov-01			
Diphtheria, tetanus, pertussis and poliomyelitis	Infanrix-IPV	NA	UA	Aug-06			
Diphtheria, tetanus, pertussis, poliomyelitis and <i>Haemophilus influenzae</i> type b	Infanrix-IPV + Hib	NA	UA	Jan-05			
Diphtheria, tetanus, pertussis, poliomyelitis and <i>Haemophilus influenzae</i> type b	Pediacel	NA	UA	Oct-02			
<i>Haemophilus influenzae</i> type b	ActHIB	Mar-03	Jan-07	Aug-92	173		46
<i>Haemophilus influenzae</i> type b and Meningococcal group C conjugate	Menitorix	NA	UA	Dec-05			
Hepatitis A and Hepatitis B	Ambirix	NA	UA	Aug-02			15
Hepatitis A and Hepatitis B	Twinrix Adult	NA	UA	Sep-96			14
Hepatitis A and Hepatitis B	Twinrix Paediatric	NA	UA	Feb-97			10
Human papillomavirus bivalent	Cervarix	Sep-07	Oct-09	Sep-07	25	25	18
Human papillomavirus quadrivalent	Gardasil	Jul-10	Jul-11	Sep-06	57	11	9
Measles, mumps and rubella (live)	MMRvaxpro	NA	UA	May-06			23
Measles, mumps and rubella (live)	Priorix	NA	UA	Dec-97			
Meningococcal group C conjugate	Meningitec	NA	UA	Sep-07			
Meningococcal group C conjugate	Menjugate	NA	UA	Mar-10			
Meningococcal group A, C, W135 and Y conjugate	Menveo	NA	UA	Mar-10			16
Pneumococcal 7-valent conjugate	Prevenar	Sep-07	Oct-09	Feb-01	104	25	16
Pneumococcal 10-valent conjugate	Synflorix	NA	UA	Mar-09			14
Pneumococcal 13-valent conjugate	Prevenar13	NA	UA	Dec-09			12

NA: not available; UA: unapproved.

^a As of March 2012.^b Represented in months.^c Approval delay was defined as the difference between the date of approval in Japan and that of first authorisation in the UK.^d Review time was defined as the time between the date of application for approval and the actual date of approval.

application and/or development. The 16 vaccines unapproved in Japan provide stronger evidence for the gap.

The term 'drug lag' [6,7] describes the launch delay of new drugs. Of the 398 new drugs approved either in the US, the EU, or Japan between 1997 and 2007, 220 (55.3%) were approved in Japan [7]; however, the percentage of approval depended on the therapeutic indication. The vaccine gap, with an approval rate only 20% (4/20) in the present study, is outstanding when compared with the much higher anti-infectives approval rate (71.4%) [7].

With the exception of meningococcal meningitis, which has an incidence of only around 10–20 cases per year in

Japan [5,23], the vaccine gap results from a complex of regulatory and social problems. We identify three here. First, vaccine regulations in Japan remain to be reformed. There are many stakeholders and governmental organisations for immunisation programmes and policies, including the Ministry of Health, Labour and Welfare (MHLW) Health Service Bureau, the Pharmaceutical and Food Safety Bureau, the PMDA, and the National Institute of Infectious Diseases. Nonetheless, there is no organisation or committee that can gather vaccine data from different areas, assess and evaluate the collected information, and present a recommendation to the government. A body that can lead

Table 2
Comparison of immunisation programme between Japan and the UK.

	Japan		UK	
	Recommendation	Coverage (%)	Recommendation	Coverage (%)
Diphtheria, tetanus, and pertussis ^a	Recommended	98	Recommended	93
Poliomyelitis ^a	Recommended ^c	99	Recommended ^d	93
<i>Haemophilus influenzae</i> type b ^a	Voluntary	ND	Recommended	93
Pneumococcal ^a	Voluntary	ND	Recommended	91
Meningococcal ^a	NA	NA	Recommended	91
Measles ^b	Recommended ^e	94	Recommended ^f	85
Rubella ^b	Recommended ^e	94	Recommended ^f	85
Mumps ^b	Voluntary	ND	Recommended ^f	85
Human papillomavirus	Voluntary	ND	Recommended ^g	87

NA: not available; ND: no official data.

^a Coverage among 1-year-olds (%) in 2008–2009.

^b Coverage among 2-year-olds (%) in 2008–2009.

^c Live attenuated oral vaccine.

^d Inactivated vaccine given as a combined vaccine with diphtheria, tetanus, and pertussis.

^e Measles and rubella, but not mumps, given as a combined vaccine.

^f Measles, rubella, and mumps given as a combined vaccine.

^g Girls of 12–13 years of age. The number represents the percentage of eligible girls receiving the first dose.

multiple organisations and propose immunisation policies [24] should therefore be established to close the gap. No regulatory guidelines existed for the clinical development and approval of vaccines in Japan before May 2010 [25]. The EU [26] and the European Federation of Pharmaceutical Industries and Associations (EFPIA) [2] have urged the Japanese government to harmonise clinical, regulatory, and technical standards for vaccines with the EU, the US, and the World Health Organization so that foreign vaccines can be imported and Japanese-produced products can be exported. An exemplary case is the polio vaccine. Japan still uses a live vaccine instead of an inactivated one, which has not been approved despite the fact that the live vaccine causes several cases of paralysis per year. On December 15, 2010, an association of polio victims submitted a petition to the MHLW, calling for approval of the importing of an inactivated vaccine. A panel of experts within the ministry also called for such an importation. The ministry's policy, however, is to wait for the four domestic makers to develop an inactivated vaccine. This obvious inaction only deepens the notion that the ministry may try to protect domestic manufacturers' vested interests [11]. Instead, the ministry should delegate vaccine-related decisions to a transparent advisory board [24].

Second, vaccine availability does not provide a single solution for overcoming the gap. The National Health Service in Japan only covers the treatment of diseases, not their prevention. In the case of vaccines covered by the Immunization Law [27], DTP, poliomyelitis, measles, and rubella vaccines are supported by governmental funds and generally provided free throughout Japan, but this does not apply to Hib, HPV, PCV, or mumps vaccines. Some local governments provide subsidies for these vaccines, but the financing policies and recipients' charges differ among these governments [12]. The inevitable consequences are regional disparities [28]. The Immunization Law should be revised to cover Hib, HPV, PCV, and mumps vaccines.

Third is the issue of public perception [29]. In Japan, as in other developed countries, fear of vaccine-preventable diseases has waned and the awareness of potential

vaccine-related risks has increased [30]. The history of the MMR vaccine in Japan provides a case study showing that negative public perception threatens vaccine acceptance.

In Japan, a high incidence of aseptic meningitis [17] followed the introduction of the MMR vaccine in 1989, which was then mandatory. The UK NHS replaced the Urabe mumps strain, which was associated with aseptic meningitis, with the Jeryl Lynn strain and avoided the problem, but the MHLW did not. A huge public outcry ensued, with a number of lawsuits against the Japanese government leading to the withdrawal of the MMR vaccine in 1993. This incident made regulators extremely wary of being sued for vaccine-related adverse events. In 1994, the MHLW revised the Immunization Law, which covered vaccines for measles and rubella but not for mumps. Today, instead of the MMR vaccine, a combined MR (measles and rubella) vaccine is provided, with the mumps vaccine being optional. The withdrawal of the MMR vaccine led to a decrease in coverage, resulting in the exportation of measles [3]. This discrimination has also led to a high incidence of mumps-associated complications in Japan [31]. Despite the availability of the MMR vaccine, the lower coverage rate of measles and rubella in the UK compared with Japan provides further evidence of the negative effect of public perception and widespread concern about the association between the MMR vaccine and autism [14].

Our study has some limitations. First, the cross-sectional observational design limits the establishment of the cause of the gap. Second, the study was based on publicly available data, which do not include subtle issues that were not captured in the deliberation process. Third, there are only a limited number of vaccines approved in Japan or in the UK. This limitation made comparisons between the two countries less conclusive. Fourth, given the heterogeneity in the vaccines considered, formal statistical analysis of the reasons for the gap was not possible.

In Japan, the vaccine programme has been planned and implemented, not on the basis of scientific evidence, but in part as a reaction to lawsuits against the government and media coverage, which has sensationalised the adverse

events and downplayed the benefits of vaccines [11,32]. Because the implementation of immunisation requires not only biological but also social, political, ethical, and economic considerations, multidisciplinary discussions should lead health professionals and the general public to be well informed about vaccines. For example, risk communication is one of the greatest challenges facing any public health authority. In Japan, there is no legal requirement for physicians to communicate the benefits and risks of vaccines to patients. Training programmes to improve physicians' knowledge and communication skills should be provided by the government.

Japan has been a leader in the development of vaccines, such as those for varicella and cellular pertussis, but the aforementioned challenges have stagnated the implementation of newly developed vaccines. We believe our proposals can contribute to a closure of the vaccine gap. The lessons learned so far have helped vaccine policy take a step forward in some respects. The UK experience of the MMR vaccine and its low coverage in urban areas [14] is a good lesson for health care professionals in Japan to improve the public perception of vaccines among Japanese citizens [32]. The Relief System for Injury to Health with Vaccination was introduced in Japan to provide relief in cases of side effects [33]. Routine immunisation is not compulsory but nonetheless high coverage rates have been achieved in Japan [34]. The international community has also contributed to closing the gap. For example, proposals in the EFPIA position paper issued in 2009 [2] had urged the Japanese government to take action to approve bivalent and quadrivalent HPV, and 7-valent PCV vaccines, which were approved in the following years. The notorious exportation [3] and outbreak of measles [35] urged the Japanese government to establish the National Measles Elimination Plan in December 2007. Recent activities among Japanese physicians to establish a strong advisory committee for vaccination policy [24] are encouraging.

5. Conclusions

The present study shows that there is still a large gap between Japan and the UK regarding access to common vaccines and immunisation programmes. The keys to closing this gap include: (1) revision of vaccine regulations, (2) amendment of the vaccine-related laws to secure funding and cooperation between professionals and public health authorities, and (3) improvement in the perception of vaccines among the general public and mass media.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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