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Eastern Mediterranean
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Agenda item 7 (b)

Technical discussions

Vaccine development, accessibility and availability: towards self-sufficiency in the Eastern Mediterranean Region
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Executive summary

Access to quality vaccines at affordable cost represents a challenge to health systems worldwide and in the WHO Eastern Mediterranean Region, in view of the few manufacturers of vaccines, the limited capabilities of national regulatory authorities and under-funded health systems, particularly in low and middle-income countries. In the Eastern Mediterranean Region, vaccines are mainly procured through the United Nations system using manufacturers prequalified by WHO. A limited proportion of vaccines used in routine and non-routine immunization programmes is produced locally by four main institutions. Most countries in the Region are not equipped with the necessary expertise in quality assurance of vaccines and most national regulatory systems do not comprise the six critical control functions established by WHO to ensure that all vaccines can be evaluated for quality and safety and released into the market for use by national immunization programmes.

Through its technical cooperation with countries, WHO has initiated a global programme to strengthen national expertise in quality assurance using a network of centres of excellence located mainly in developed countries. The Eastern Mediterranean Region has benefited from such training opportunities and is expanding its critical mass of experts in the field of quality assurance of vaccines. WHO has also launched an assessment of national regulatory authorities globally and in the Region, while helping countries to better assess their vaccine needs.

In view of the importance of self-sufficiency and self-reliance in vaccines in the Eastern Mediterranean Region, WHO is assessing the vaccine manufacturers of the Region in terms of their viability, production possibilities and their needs in terms of capacity-building and research and development. Of the four vaccine-producing countries in the Region, only Egypt and the Islamic Republic of Iran are self-sufficient in the local production of traditional vaccines and other immunizing agents and have export potential. Some vaccine producers in the Region are also developing cutting edge technology, including biotechnology and recombinant vaccines and are initiating, with government support, research and development activities.

Because of the importance of national and regional vaccine security, the Regional Office is proposing to establish a regional programme on self-sufficiency and self-reliance in vaccines and is developing its partnerships with development banks, including the African Development Bank, the Islamic Development Bank and the World Bank, in order to secure necessary resources for programme implementation. A new unit on technical support to quality of vaccines has been established in the division of health systems and services development and is aimed at strengthening capacity-building in national regulatory authorities, at improving horizontal cooperation between vaccine-producing countries in the Region and with other regions, and at coordinating their input to regional vaccine production. The regional programme will focus first on vaccines used as part of the EPI schedule and will concentrate on strengthening national regulatory capabilities. WHO will continue its efforts to help countries achieve self-reliance in financing and sustainability of vaccine production and procurement.
1. **Introduction**

Vaccines are important tools in disease prevention programmes and their availability at good quality and at affordable cost represents a challenge for health systems, particularly in developing countries. New global changes and challenges, including increased competition, difficulties in accessing cutting edge technology, reduction in the number of vaccine suppliers, limited market and profit margins and decreased interest in vaccine production by the industrialized countries, are putting additional strains on self-sufficiency initiatives. The multinational manufacturers who have traditionally supplied a large proportion of the vaccines of WHO’s global Expanded Programme on Immunization (EPI), which targets the killer diseases of childhood, are now diverting their business to more profitable products. This move has created a void for EPI vaccines, which is being filled by manufacturers from developing countries. In 1992, 100% of the vaccines purchased by UNICEF came from the industrialized countries; in 2000, 53% came from developing countries. 65% of all BCG vaccine and 56% of all measles vaccine produced globally are manufactured in India and Indonesia [1]. Several vaccine manufacturers have either closed down their facilities or have merged, thus reducing the total number of manufacturers. Moreover, 7 out of 10 producers of measles vaccine have left the business in recent years or have merged, thus creating a monopoly for a single manufacturer, which has dangerous implications.

The process of building regulatory capacity is based on the implementation of an independent national regulatory system comprising the following six critical control functions established by WHO to ensure that all vaccines can be evaluated for quality and safety and released into the market for use by national immunization programmes.

1. A published set of clear requirements for licensing (of products and manufacturers), or marketing authorization (MA) and activity licensing
2. Surveillance of vaccine field performance (safety and efficacy), or post-marketing surveillance including adverse events following immunization (AEFI)
3. System of lot release, or national regulatory authority lot release
4. Use of laboratory when needed, or laboratory access
5. Regular inspections of manufacturers for compliance with good manufacturing practices (GMP), or regulatory inspection
6. Evaluation of clinical performance, or authorization/approval of clinical trials

An effective vaccine regulatory system is based on the principle that vaccine quality is primarily the responsibility of the manufacturer. However, it is the responsibility of the government to oversee the entire production process and to provide the continuing evidence for quality, safety and efficacy of the vaccine through a competent and independent national regulatory authority, both for vaccines to be used within the country, and for those to be exported. Finally, the vaccine procurer must build in, as part of the purchase agreement, a guarantee of quality. This includes developing appropriate specifications and assurance of good distribution and handling. Thus quality is the responsibility of all those involved in the immunization system.

The number of regulatory functions required by the national regulatory authority to guarantee the quality of vaccines will depend on the individual country and whether vaccines are procured through UNICEF, procured through the Ministry of Health or manufactured locally. All countries must have the critical function of a regulatory system, and dependent on procurement practices, other functions must be implemented by the national regulatory authority. In the case of the vaccine-producing countries they must meet all the functions, especially if they plan to export the product or make it available to UN Agencies.

Since 1990, the global pattern for sourcing of vaccines has evolved. In 2003, of 192 Member States of WHO, 48 were producing countries, 83 countries procured through UNICEF and 61 procured directly from manufacturers. This represents a reduction (since 1990) in the number of producing countries...
(from 63 to 48) and in the number that procure from UNICEF (from 102 to 83), and an increase in direct procurement (from 26 to 61). In 2002, 30 out of the 48 producing countries had implemented a fully functional vaccine regulatory system.

Many of the products produced by manufacturers in developing countries fulfil all the conditions established by WHO in its system of prequalification, thus meeting all the requirements for assured quality. However, the shift in production from the industrialized to the developing countries has created a situation that requires strategic thinking with regard to self-sufficiency and procurement of vaccines for WHO’s Eastern Mediterranean Region. Countries of the Region rely mainly on importation to meet the needs of their immunization programmes. Four countries of the Region have vaccine production capabilities that would allow for self-sufficiency in vaccine production in the Region as a whole.

Self-sufficiency may be defined as a country’s ability to provide an adequate and reliable supply of affordable high quality vaccines against priority diseases now and for the future [2]. The regional goal must be that 100% of the vaccines used in the national immunization programmes are of assured quality. Quality is defined as assured when the national regulatory authority has a regulatory system in place and is compliant with the functions necessary to reflect the national procurement and sourcing of vaccine and there is no unresolved problem with vaccine manufactured.

In this paper, vaccine production in the Eastern Mediterranean Region is assessed, highlighting the main issues and requirements for improvement. The main elements of a regional strategy aimed at ensuring self-sufficiency in vaccine production are proposed, with focus on the need for support for the national regulatory authorities.

2. Situation analysis

2.1 Procurement of vaccines within the Eastern Mediterranean Region

The implementation of any immunization programme must be within the context of ongoing public health policy. Health sector reform is sweeping through many countries in the Region. The opportunities and challenges presented by reforms need to be evaluated in the context of vaccine security, research and development, and vaccine regulation. Immunization programmes cannot function in isolation. Consequently, the capacity to integrate with other programmes needs to be developed.

A total of 10 antigens are currently used by national EPI programmes in the Region: BCG, diphtheria, tetanus, whooping cough, polio, measles, mumps, rubella, hepatitis B and *Haemophilus influenzae* b. These antigens are either provided as monovalent vaccines or combined with other antigens, resulting in 13 types (Box 1).

BCG, OPV, DPT, measles and TT are used by all countries in the Region. A previously under-used HepB vaccine is in use in all countries except Afghanistan, Djibouti and Somalia (which have less than 50% coverage of target infants with the basic vaccines). The necessary groundwork for introducing any new vaccine includes reviewing data or conducting burden of disease studies, addressing cold chain challenges, integrating the use of auto-disable (AD) syringes and assessing the global supply situation. Burden of disease assessments and surveys made in the Region show that *Haemophilus influenzae* b diseases are moderate to highly prevalent in almost all the Region except in Afghanistan, Islamic Republic of Iran and Pakistan. Accordingly, this highly cost-effective and safe vaccine should be introduced in all remaining countries except those three remaining Member States (19). To date only 10 countries have introduced it. The main reasons behind this slow uptake are the cost of the vaccine and lack of awareness. The Regional Office is committed to ensuring that all children living in the Region benefit from these two highly effective and safe vaccines as soon as possible.
Box 1. Types of antigens used by EPI programmes in countries of the Eastern Mediterranean Region

- **BCG**
- **OPV** (oral poliovaccine)
- **DPT** (diphtheria, pertussis and tetanus vaccine)
- **M** (measles monovalent vaccine)
- **HepB** (hepatitis B vaccine)
- **TT** (tetanus toxoid)
- **Td** (tetanus toxoid + diphtheria for persons > 6 years old)
- **DT** (diphtheria for children < 6 years + tetanus toxoid)
- **Hib** (*Haemophilus influenzae* b monovalent vaccine)
- **MMR** (combined measles, mumps and rubella vaccine)
- **DPT–HepB** (quadrivalent vaccine = combined DPT and hepatitis B vaccine)
- **DPT–Hib** (quadrivalent vaccine = combined DPT and *haemophilus influenzae* b vaccine)
- **DPT–HepB–Hib** (pentavalent vaccine = combined DPT, HepB and Hib)

Currently more and more countries are choosing the option of combination vaccines, which is an attractive option, as well as the future of the vaccination programmes. Eleven countries have already shifted to either DPT–HepB–Hib, or DPT–Hib or DPT–HepB; and 11 countries are using MMR vaccine.

Reports from 18 countries show that in 2003, a total of 590 million doses of vaccines were purchased in the Region, only 12.5% of which were from local producers (Table 1). It is important to note that 87.5% of vaccines used in the Region are purchased through UNICEF or are procured from outside the Region from WHO pre-qualified vaccine producers, through the Ministry of Health.

### Table 1. Source of vaccines used in the Eastern Mediterranean Region in 2003

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Total doses purchased in 2003</th>
<th>From local manufacturers</th>
<th>Through UNICEF</th>
<th>Self-purchase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doses</td>
<td>%</td>
<td>Doses</td>
<td>%</td>
</tr>
<tr>
<td>BCG</td>
<td>32 767 000</td>
<td>28.3</td>
<td>19 688 000</td>
<td>60.1</td>
</tr>
<tr>
<td>OPV</td>
<td>391 390 790</td>
<td>8.2</td>
<td>316 697 000</td>
<td>80.9</td>
</tr>
<tr>
<td>DTP</td>
<td>38 993 700</td>
<td>20.5</td>
<td>28 202 700</td>
<td>72.3</td>
</tr>
<tr>
<td>Measles</td>
<td>30 622 666</td>
<td>23.7</td>
<td>20 813 500</td>
<td>68.0</td>
</tr>
<tr>
<td>HepB</td>
<td>30 887 618</td>
<td>64.0</td>
<td>19 759 141</td>
<td>64.0</td>
</tr>
<tr>
<td>TT</td>
<td>27 507 829</td>
<td>72.3</td>
<td>17 889 500</td>
<td>65.0</td>
</tr>
<tr>
<td>Td</td>
<td>10 596 840</td>
<td>66.1</td>
<td>2 096 000</td>
<td>19.8</td>
</tr>
<tr>
<td>DT</td>
<td>994 700</td>
<td>72.0</td>
<td>72 000</td>
<td>7.2</td>
</tr>
<tr>
<td>Hib</td>
<td>673 400</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>MMR</td>
<td>8 843 631</td>
<td>41.3</td>
<td>3 650 000</td>
<td>41.3</td>
</tr>
<tr>
<td>DPT–HepB</td>
<td>7 229 000</td>
<td>93.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>DPT–Hib</td>
<td>7 947 700</td>
<td>41.1</td>
<td>3 266 700</td>
<td>41.1</td>
</tr>
<tr>
<td>DPT–HepB–Hib</td>
<td>831500</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>589 286 374</td>
<td>12.5</td>
<td>432 134 541</td>
<td>73.3</td>
</tr>
</tbody>
</table>

Source: WHO/UNICEF Joint Reporting Forms 2003 (covers all Member States except Djibouti, Iraq, Kuwait and Palestine, which had not reported at the time of writing)

The huge quantity of polio vaccine is mainly due to the intense supplementary immunization activities conducted in some countries, such as Afghanistan, Egypt, Pakistan and Somalia.
<table>
<thead>
<tr>
<th>Year</th>
<th>BCG</th>
<th>DTP</th>
<th>MCV</th>
<th>MMR</th>
<th>OPV</th>
<th>Hib</th>
<th>HepB</th>
<th>TT</th>
<th>DPT–HepB</th>
<th>DPT–Hib</th>
<th>DPT–HepB–Hib</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>18 383 610</td>
<td>45 470 001</td>
<td>16 437 590</td>
<td>9 852 840</td>
<td>76 232 281</td>
<td>7 829 947</td>
<td>21 438 762</td>
<td>32 681 973</td>
<td>6 759 138</td>
<td>8 980 944</td>
<td>865 280</td>
</tr>
<tr>
<td>2004</td>
<td>18 801 758</td>
<td>46 491 847</td>
<td>16 807 704</td>
<td>10 067 611</td>
<td>77 921 403</td>
<td>9 895 345</td>
<td>22 192 326</td>
<td>33 425 347</td>
<td>6 894 321</td>
<td>9 192 517</td>
<td>888 685</td>
</tr>
<tr>
<td>2005</td>
<td>19 230 138</td>
<td>47 538 945</td>
<td>17 188 760</td>
<td>10 287 722</td>
<td>79 651 434</td>
<td>10 111 552</td>
<td>22 707 008</td>
<td>34 186 912</td>
<td>7 032 207</td>
<td>9 409 634</td>
<td>912 725</td>
</tr>
<tr>
<td>2006</td>
<td>19 669 020</td>
<td>48 611 976</td>
<td>17 574 990</td>
<td>10 513 324</td>
<td>81 423 451</td>
<td>10 332 992</td>
<td>23 235 483</td>
<td>34 967 146</td>
<td>7 172 851</td>
<td>9 632 455</td>
<td>937 416</td>
</tr>
<tr>
<td>2007</td>
<td>20 118 681</td>
<td>49 711 637</td>
<td>17 972 632</td>
<td>10 744 567</td>
<td>83 238 559</td>
<td>10 559 812</td>
<td>23 778 164</td>
<td>35 766 543</td>
<td>7 316 308</td>
<td>9 861 142</td>
<td>962 777</td>
</tr>
<tr>
<td>2008</td>
<td>20 579 406</td>
<td>50 838 649</td>
<td>18 379 929</td>
<td>10 981 612</td>
<td>85 097 896</td>
<td>10 792 167</td>
<td>24 335 478</td>
<td>36 585 610</td>
<td>7 462 634</td>
<td>10 095 863</td>
<td>988 826</td>
</tr>
<tr>
<td>2009</td>
<td>21 051 488</td>
<td>51 993 752</td>
<td>18 797 135</td>
<td>11 224 619</td>
<td>87 002 632</td>
<td>11 030 218</td>
<td>24 907 866</td>
<td>37 424 868</td>
<td>7 611 887</td>
<td>10 336 793</td>
<td>1 015 582</td>
</tr>
<tr>
<td>2010</td>
<td>21 535 231</td>
<td>53 177 709</td>
<td>19 224 505</td>
<td>11 473 758</td>
<td>88 953 970</td>
<td>11 274 130</td>
<td>25 495 784</td>
<td>38 284 855</td>
<td>7 764 125</td>
<td>10 584 109</td>
<td>1 043 063</td>
</tr>
</tbody>
</table>

**Table 2.** Estimated vaccine requirements for the routine EPI programmes in all countries of the Eastern Mediterranean Region, 2003–2010

| Total (rounded to million doses) | 159 | 394 | 142 | 85 | 660 | 82 | 188 | 283 | 58 | 78 | 8 |

MCV measles-containing vaccine
Table 2 shows the estimated vaccine requirements for routine immunization in all countries of the Region for the period 2003–2010 inclusive. Estimates are based on the following:

- current routine immunization schedules
- current antigens and type of vaccines in use in countries and taking into consideration changes already decided upon (i.e. HepB vaccine introduction in Sudan in mid 2004 and pentavalent vaccine introduction in Yemen and Egypt in early 2005); and
- assumptions of 90% coverage, stable demographic indicators (population growth rate, crude birth rate and infant mortality rate), and 25% wastage for multi-dose vaccines;
- supplementary immunization activities (polio national immunization days, measles campaigns, etc) were not included.

2.2 Priority new vaccines

The use of newly available vaccine options, such as HepB, remains a big challenge. However, there are other killer diseases that now take a huge toll on productive lives and for which no safe, effective and economical vaccines yet exist. Many of these diseases, such as acute respiratory infections (ARI), diarrhoea, tuberculosis, malaria and HIV/AIDS, affect the Region (Table 3).

Developing and marketing a new vaccine can take up to 15 years and cost US$ 500 million or more [3]. While the industrialized countries tend to have resources available for both preventive and curative programmes, drugs and even low-cost prevention measures are less available in developing countries, because of limited resources and multiple competing health problems. At the same time, since the large burden of most of these killer diseases occurs in developing countries, the levels of investment in vaccine research and development in the industrialized countries are limited because manufacturers have little commercial incentive to develop the vaccines. The current situation with regard to priority new vaccines to tackle these diseases is as follows.

Pneumococcal vaccine

A 7-valent conjugate vaccine has already been licensed and is in use in several countries in Europe and the Americas, as well as in Australia. This vaccine has demonstrated high efficacy and has proved to be very safe. However, the vaccine does not include key serotypes that are prevalent in developing countries. More types (9-valent and 11-valent) are currently in the pipeline. The regional priority is currently to identify the most frequent and virulent types in the Region and to document the disease burden [3].

Rotavirus vaccine

A genetically engineered vaccine was developed and licensed in the USA in 1998 and several other candidate rotavirus vaccines are currently in the pipeline. The regional focus is currently on documenting the rotavirus disease burden and conducting cost-effectiveness studies, in order to raise awareness and prepare for vaccine introduction [3].

<table>
<thead>
<tr>
<th>Disease or infectious agent</th>
<th>*Global cases 2000 (million)</th>
<th>*Global deaths 2001 (million)</th>
<th>Eastern Mediterranean Region deaths (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI</td>
<td>&gt; 70</td>
<td>3.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>&gt; 900</td>
<td>2.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>8</td>
<td>1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Malaria</td>
<td>300–500</td>
<td>1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>5</td>
<td>2.9</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Tuberculosis**

The existing tuberculosis vaccine, BCG, protects only against miliary tuberculosis and tuberculous meningitis in the first year of life. Global efforts are in progress to develop *Mycobacterium tuberculosis*-derived vaccines and candidates of this new generation of vaccines could be developed by 2012–2015 [3].

**Malaria**

Over the past decade, there has been significant progress in malaria vaccine development, yet many valid candidate vaccines have been slow to enter clinical trials and an effective vaccine is thought be at least 10 years away.

**HIV/AIDS**

While much more basic research is still needed, a successful vaccine against HIV is believed to be scientifically possible. However, this optimism is tempered by continued under-investment in HIV vaccine development. Currently, around 19 HIV candidate vaccines are at different levels of clinical testing in Europe, the USA and elsewhere.

### 2.3 Regional vaccine production

There are four vaccine-producing countries in the Region: Egypt (VACSERA), Islamic Republic of Iran (Razi and Pasteur Institutes), Pakistan (National Institute of Health) and Tunisia (Pasteur Institute). They produce various EPI and non-EPI vaccines, sera and other products, including syringes (Table 4). Egypt and Islamic Republic of Iran have a large production capacity resulting in national

| Table 4. Vaccine producing countries in the Region |
|---------------------------|-----------------|-----------------|-----------------|
| **Country**               | **Vaccine**     | **Production 2003** | **Current production capacity** | **Future production capacity 2010** |
| Egypt                     | BCG             | 4 million doses   | 30 million doses | 50 million doses |
|                           | DPT             | 30 million doses  | 60 million doses |  |
|                           | Measles         | 70 million doses  | 300 million doses (vial) | 400 million doses (plastic tubes) |
|                           | OPV             | 15 million doses  |  |
|                           | Tetanus toxoid  | 5 million doses   | 30 million doses (vial) | 30 million doses (vial) |
|                           | Hep B           | 150 million doses (vial) | 6 million doses (Unject) |  |
|                           | DTP-Hep B       | 4.01 million doses | 20 million doses | 20 million doses |
|                           | DT              | 4.01 million doses | 27 million doses |  |
|                           | Meningitis      | 4.01 million doses |  |
| Islamic Republic of Iran  | BCG             | 25 million doses  |  |
|                           | DPT             | 3.5 million doses | 6 million doses | 25 million doses |
|                           | Measles         | 27.116 million doses | 35 million doses | 35 million doses |
|                           | OPV             | 60 341 doses       | 6 million doses |  |
|                           | Tetanus toxoid  | 60 341 doses       |  |
|                           | Hep B           | 20 million doses   |  |
|                           | DTP-Hep B       | 25 million doses   |  |
|                           | DT              | 0.5 million doses  |  |
| Tunisia                   | BCG             | 2 million doses    | 10 million doses |  |
|                           | DPT             |  |
|                           | Measles         |  |
|                           | OPV             |  |
|                           | Tetanus toxoid  |  |
|                           | Hep B           |  |
|                           | DTP-Hep B       |  |
|                           | DT              |  |
self-sufficiency for some vaccines and allowing the export of some products. It is estimated that the current capacity can cover nearly all the needs of the Region for EPI vaccines well into 2006, except for BCG vaccine. However, this shortfall in BCG is expected to be met soon as two countries in the Region are building new BCG facilities.

Regional producers need to have a clear strategy based on their comparative technical advantage and should take into consideration the needs of the whole Region. Well designed coordination and division of labour between vaccine-producing countries, and avoidance of duplication, is essential to cost-effective production.

Taking into consideration the increasing number of antigens that have to be given to children at the same time, as well as the risks inherent in injection practices, more and more combination vaccines are expected in the future and the use of combination vaccines will become the main option for vaccine programmes. Combination vaccines containing hepatitis and \textit{haemophilus} vaccines together with DTP vaccine are now routinely available, and these are slowly moving into the EPI programmes. One of the four regional vaccine producers is actively pursuing this direction and this is to be encouraged as it will further strengthen self-sufficiency in the Region.

Some of the vaccine producers in the Region are also developing cutting edge technology, including biotechnology and recombinant vaccines and are initiating with government support, research and development activities. As research and development is generally not well supported in the Region, some producers are finding it difficult to gain access to advanced technology in vaccine production. Exchange of expertise between countries of the Region and Indonesia and Malaysia, for example, could facilitate technological improvement. Some countries also have difficulty gaining access to training for political reasons.

Of the four main manufacturers it is considered that three could meet the requirements for viability set by WHO. This is based on a very rough estimate and the Regional Office needs to consider full assessment of the viability of these three manufacturers and consider supporting them as part of the strategic plan for vaccine self-sufficiency. Economic and financial factors, including reduction of vaccines prices and need for subsidy, will need to be taken into account.

### 2.4 Status of national regulatory authorities

As already noted in the introduction, all vaccines used within national immunization programmes must meet WHO prequalification requirements for quality and safety. To assure the quality and safety of vaccines, countries must have in place a system of licensing for the product and product facilities, surveillance for the vaccine performance in field conditions, a system of lot release, use of laboratory testing when needed, regular inspection and compliance with good manufacturing practice (GMP) and evaluation of clinical trial data in licensing decisions.

WHO teams have assessed the situation of the national regulatory authorities in nine countries of the Region. Only three meet the WHO requirements for a functional national regulatory authority, Oman, Saudi Arabia and Tunisia, of which only Tunisia is a vaccine-producing country. The other 13 countries need to be assessed for their compliant status.

Where regional manufacturers have upgraded their facilities to meet GMP standards, they face frustration that the national regulatory authorities in their countries do not meet the requirements of the six critical control functions, thus limiting their capabilities to export or to have their products prequalified by WHO. It is important that the four vaccine-producing countries are supported in their efforts to upgrade their national regulatory authorities, and priority should be given to the national regulatory authorities in countries where manufacturers have demonstrated GMP implementation within their facilities and are deemed viable.
3. WHO initiatives to support self-sufficiency in vaccine production

3.1 National regulatory authority strengthening

History has shown that weak regulatory oversight has a negative impact on public health by resulting in poor quality, unsafe, ineffective and or non-efficacious products and inadequate information for the use of the product. Some 23% of infants are at risk globally, because regulatory systems are unable to guarantee that vaccines manufactured or procured are of assured quality, and the six regulatory functions recommended by WHO are not independently and competently exercised by the national regulatory authorities. The deficiency of national regulatory authorities raises serious issues with regard to the safety and efficacy of vaccines and is a new challenge for governments (including those in the Eastern Mediterranean Region), patients, health professionals and WHO. It is clear that regional efforts must be expanded to ensure the national regulatory authorities of the four vaccine-producing countries in the Region meet the required functions.

In 1990 WHO developed a matrix for all 192 Member States of WHO, based primarily on the source of vaccines, in order to determine priority needs for strengthening of national regulatory systems. At that time, no assessments of national regulatory authorities were being conducted, very few regulatory systems were well documented and none of them implemented all the regulatory functions. The main sources of vaccines were UNICEF (102 countries), local production (63 countries) and procurement (26 countries). Subsequently, a definition of assured quality vaccine was developed in order to monitor the quality of vaccines in all countries. The definition of an assured quality vaccine presupposes an independent, fully functional national regulatory authority, and no unresolved reported problem with a vaccine. The priority matrix guides countries to develop their regulatory system according to the source of vaccines. For countries which obtain their vaccines mainly from UNICEF, only two functions are required (licensing and surveillance of AEFI). When vaccines are procured directly from the manufacturers, two additional functions are recommended (lot release and laboratory access). For vaccine-producing countries GMP inspections and clinical evaluation of safety and efficacy are necessary (Table 5).

In order to achieve these goals, a five-step capacity-building process has been developed that includes: 1) benchmarking against a published set of indicators; 2) conducting national regulatory authority assessments; 3) planning to address gaps; 4) implementation of a national regulatory authority institutional development plan including technical input provided through the global training network (GTN); and 5) monitoring and evaluation of recommendations to address gaps and measure impact.

The capacity-building process is based on a 5-day national regulatory authority audit conducted by an international team of vaccine regulatory experts. During the visit an in-depth review is conducted of the functions of the national regulatory authority; gaps, training needs and specific technical support needs are identified and a plan for follow up is developed. The report is submitted to the national regulatory authority which must endorse all recommendations before WHO can provide its guidance and support. The capacity-building is promoted by the use of national expertise to conduct national regulatory authority assessment and by exposing national staff to new regulatory issues and involving them in planning to address those issues. All national regulatory authority assessments are closely coordinated with funding partners and regional offices to ensure that appropriate support is available. So far 49 national regulatory authority assessments have been conducted and all Regions are participating in this process. The assessments started with the development of national regulatory authority indicators in 1998, with input from 38 countries. All producing countries were then targeted for assessment with the initial objective of targeting primarily all countries with prequalified vaccines.

Table 5. Critical control functions depending on vaccine source

<table>
<thead>
<tr>
<th>Vaccine source</th>
<th>Licensing</th>
<th>Surveillance</th>
<th>Lot release</th>
<th>Laboratory access</th>
<th>GMP inspections</th>
<th>Clinical evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Nations agency</td>
<td>×</td>
<td>×</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>Procure</td>
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<td>×</td>
<td>×</td>
<td>×</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Produce</td>
<td>×</td>
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<td>×</td>
<td>×</td>
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</tr>
</tbody>
</table>
3.2 Global training networks

A global training network (GTN) was established in 1996 to support regulatory capacity-building for the national regulatory authorities, vaccine manufacturers and EPI staff. The network comprises 13 training centres which provide training courses in more than 10 areas related to vaccine quality. More than 500 staff have been trained from 76 countries, including countries of the Eastern Mediterranean Region. Such training has contributed to the development of a critical mass of professionals serving in their respective countries. Twelve experts from the Region have also contributed to capacity-building in other developing countries, inside and outside the Region.

3.3 Technical cooperation among developing countries in vaccine production

WHO’s Regional Office for the Eastern Mediterranean has supported streamlining collaboration between the four regional producers, and has initiated a very fruitful collaboration between vaccine producers in the Islamic world. The strong commitment of the Regional Director to this collaboration facilitated the signing of a trilateral agreement between Indonesia, Islamic Republic of Iran and Pakistan in 2002 by their respective Ministers of Health, aimed at encouraging the exchange of technical expertise in vaccine production and at providing preferential commercial support. Bio Farma of Indonesia, a pre-qualified manufacturer for both viral and bacterial vaccines, is expected to become an instrumental partner in this initiative. This collaboration could be expanded to include Egypt and Tunisia.

The need to strengthen horizontal cooperation between vaccine producers in Islamic countries was echoed in a meeting of Islamic vaccine producers convened by the Islamic Development Bank in Tunis (13–15 March 2004).

3.4 Strengthening regional technical support in vaccine production

Because of the importance of self-sufficiency in vaccine production and the growing needs expressed by countries of the Region for technical assistance, the Regional Director has decided to establish a technical unit in the Regional Office responsible for quality improvement in vaccine production. The new unit is expected to further expand the capacity-building programme supported by WHO headquarters and the global training network and to focus on strengthening national regulatory authorities and on technical cooperation between countries of the Region. The unit will also liaise with the Islamic Consortium of Vaccine Producers, with other WHO regional offices and with development banks supporting vaccine production in the Region.

3.5 Partnership with development banks for self-sufficiency and self-reliance in vaccine production

Resolution 35-8 of the Eighth Islamic Summit Conference held in Teheran in December 1997 laid down the objectives and principles of enhancing collaboration between vaccine producers in the field of training, exchange of expertise and quality control and improvement systems. A programme to achieve self-reliance in vaccine-production for the Islamic countries was developed by the Islamic Development Bank in 1999 and a grant of a US$ 5.6 million was allocated for its implementation. Seed money was earmarked for the following activities:

- co-operation between vaccine producers in research and development
- training of staff
- improvement of quality assurance and quality control
- initiation of feasibility studies
- upgrading of production facilities
- cooperation between producers in sales and marketing.

Technical teams were fielded to Egypt, Indonesia, Islamic Republic of Iran and Tunisia to assess existing vaccine production facilities, to assess GMP, to identify training needs in order to comply with WHO requirements for quality assurance and improvement, and to assess needs for physical
upgrading and eventual introduction of new vaccines. Training was provided for fellows from Islamic countries by Bio Farma of Indonesia, the National Institute of Public Health and the Environment of the Netherlands and the International Vaccine Institute of Korea.

Four proposals from Algeria, Egypt, Islamic Republic of Iran and Tunisia, amounting to US$ 1.2 million were financed through the grant. The proposals included capacity-building in vaccine production-related areas and feasibility studies to upgrade existing facilities and to establish new functions [4].

A network of vaccine producers from Islamic countries was created and held its first meeting in Egypt in September 2000. The meeting highlighted the need to develop a consortium of vaccine producers in the Islamic world and to cooperate in the fields of manufacturing, research and marketing. Annual meetings were held in Bandung, Indonesia, in 2001 and in Jeddah, Saudi Arabia in 2002 and 2003. At the 2003 meeting of the network important decisions were taken in line with the objective of improving self-sufficiency and self-reliance in vaccine production. A website will be developed in order to allow for faster information sharing between vaccine producers, and focal points for training and technology transfer were nominated. A webmaster from VACSERA, Egypt, was identified to feed the website with necessary information. At the 2004 meeting held in Tunis, Tunisia, participants called for an active role for the Islamic Development Bank in fund raising for self-sufficiency in vaccine production, and for strengthening of WHO’s technical assistance in capacity-building and in brokering financial support from donors and development banks [4].

4. Proposed strategic approaches to self-sufficiency in vaccine production of assured quality and safety

4.1 Assessing needs and planning

Countries of the Region should initiate forecasting to determine needs for various vaccines in the medium term and long term, taking into consideration the inclusion of new vaccines in their immunization programmes and the new developments in vaccine production. Such forecasting exercises should be linked to priority health programmes resulting from the disease burden and epidemiological profile. WHO can provide support in estimating the needs of the countries of the Eastern Mediterranean Region.

Vaccine producers in the Eastern Mediterranean Region should identify their comparative advantage in vaccine production, including areas of specialization and existing expertise and their production potential for the various lines. The Regional Office, in collaboration with the network of vaccine producers, could play a coordinating role in defining some division of labour among producers in order to avoid duplication in vaccine production and to increase economic efficiency. The network of vaccine producers from Islamic countries could develop scenarios for meeting the objective of self-sufficiency in vaccine production.

A complete evaluation of the needs of the facilities and costs associated with refurbishment of manufacturing capacity is necessary and should be initiated and completed as soon as possible.

Regional needs for capacity-building in areas related to vaccine production, including development of regulatory functions and quality assurance and control, should be assessed. Centres of excellence, inside and outside the Region, that can be used in capacity-building, should be identified. Bio Farma of Indonesia, the National Institute for Natural Products, Vaccines and Biologicals of Malaysia and three regional producers (VACSERA, Egypt, Pasteur Institute, Islamic Republic of Iran and Pasteur Institute, Tunisia) may be considered in this respect. Other regional manufacturers should be further strengthened.

4.2 Development of a regional programme to strengthen self-sufficiency in vaccine production

Following situation analysis, a regional programme to strengthen self-sufficiency in vaccine production should be developed by the Regional Office in collaboration with WHO headquarters and
other partners, including other WHO regions, the network of vaccine producers and development banks. Such a programme should have a three-point strategy:

- capacity-building (training of staff, provision of expertise, institutional development)
- information sharing and coordination between vaccine producers in the Region
- promotion of research and development.

Training through the GTN for national regulatory authority compliance should be encouraged both for vaccine-producing and non-vaccine-producing countries. Capacity-building should include auditing of national regulatory authority compliance, and should promote collaboration with national regulatory authorities outside the Region (such as Indonesia), in order to upgrade national regulatory authorities. Training programmes could start by early 2005.

Within a period of 3–5 years all countries within the Region should meet the WHO prequalification requirements. The Region has the know-how and capability to meet this challenge; however it will need technical, financial and regulatory support, either through direct WHO intervention or collaboration with other vaccine producers outside the Region.

The regional programme should also include an element for advocacy in order to mobilize necessary financial resources to achieve self-sufficiency objectives. The high rate of return of investment in biotechnology will facilitate the advocacy role of WHO and other partners to attract potential private investors from the Region.

4.3 Promoting investment in vaccine production in the Region

Capital infusion to upgrade the manufacturing facilities will be essential to meet WHO prequalification requirements. WHO can provide technical support to manufacturers in their proposals for financial support from the Islamic Development Bank, the World Bank or local financial institutions. Viability studies should be conducted for three of the four main manufacturers to allow for evaluation of sustainability. Grants from the Islamic Development Bank could be used for implementing such economic and technical evaluations.

4.4 Targeting priority interventions of the self-sufficiency initiative

The focus of the regional self-sufficiency initiative should be on strengthening national regulatory systems through the national regulatory authorities in the four vaccine-producing countries. The national regulatory authorities of these countries must become compliant with the six critical control functions which will pave the way for prequalification of the manufacturers. WHO’s priority must lie in supporting producing countries to achieve national regulatory authority compliance, after which support can be extended to manufacturers. It should be possible to get this compliance for some of the national regulatory authorities within a period of one year if a committed effort is involved. However, all the other vaccine-producing countries should be compliant within two years.

National regulatory authorities of non vaccine-producing countries should become compliant with the functions as required by their procuring practices. As only three countries of the Region are compliant, the remaining countries should be encouraged to become compliant also. This objective can be achieved in 3-5 years within the Region, with 90% compliance.

4.5 Biotechnology and vaccine development

Recent advances in biotechnology have opened up a new era for vaccines development. Genetic engineering and gene manipulation have made it possible to produce live attenuated vaccines, which are non-pathogenic, by deletion of specific genes. The knowledge of the entire genomic sequence of pathogenic viruses and bacteria will make the production of such vaccines possible.

Recombinant technology is offering new methods for producing new types of vaccines. For example, fusion vaccine, such as contraceptive fusion vaccine, is a new type of vaccine that provides good potential for planning pregnancy, particularly in developing countries. New vaccine technologies
include genetically improved live vaccines, such as genetically attenuated micro-organisms and live vector vaccines; anti-idiotypic antibody vaccines; synthetic peptide-based vaccines; and nucleic acid vaccines. With the exception of synthetic peptide vaccines, other types of new vaccines are produced in the following technological steps: cultivation, downstream and pharmaceutical formulation.

It is therefore important to emphasize the fact that production of new vaccines requires strict compliance to rigorous GMP rules to minimize lot-to-lot variations. It is important to develop national and regional expertise in new biotechnology techniques, including modern analytical techniques required to develop and produce priority new vaccines [5].

5. Conclusion

In view of the global changes and challenges facing health systems in better achieving their intrinsic goals of improving health and reducing health inequalities in an equitable and responsive way, self-sufficiency in vaccine production is of utmost importance. Indeed, access to quality and affordable vaccines is an important component of health security for countries and regions and deserves to capture the interest of policy-makers. Such access is vulnerable to the knowledge divide between industrialized and developing countries, and the changing health scenarios in the former and subsequent lack of interest in developing some vaccines with no or limited domestic use.

Aware of these concerns, many developing countries (such as Cuba and Indonesia) started developing their vaccine production capabilities and have achieved high standards, allowing them to export to the industrialized countries and to United Nations procuring agencies. Some countries are investing in advanced bio-technology, which will have implications for vaccine and medicines development in the near future.

The Eastern Mediterranean Region is fortunate to have a number of large-scale manufacturers that can probably meet the Region’s self-sufficiency needs. However, these manufacturers have historically focused on the manufacture of vaccines simply to meet the demands of their country, without exploring other market needs. In many instances these manufacturers have excess capacity which would support the needs of the Region, thus allowing for sustainability of their own operations.

Unfortunately none of these manufacturers are pre-qualified by WHO, either because their national regulatory authorities are not compliant with the established criteria or because their facilities do not meet the current GMP requirements. These obstacles can be overcome and the products from these manufacturers made pre-qualifiable. This will require technical and financial support and WHO can provide the necessary technical support to proposals for financial support from appropriate financial institutions. The focus of WHO’s technical support should be on developing necessary expertise and on institutional development, particularly with respect to the regulatory functions.

In view of the strategic role of vaccines in health protection and prevention programmes, self-sufficiency in vaccine production needs strong political commitment from governments through ministries of health and related ministries and agencies.

References


