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LECTURE NOTES

Burden of vaccine-preventable diseases: News and epidemiological updates

Preben Aavitsland at EPCM, University of Basel, 3.9.2015

Summary

In this lecture at the University of Basel, Preben Aavitsland discusses vaccines and vaccine-preventable diseases, with an emphasis on disease burden.

These notes are not a word for word manuscript, but rather a combination of the slides and some main points from the lecture.

Introduction

Thank you for inviting me. I will share some facts and views on vaccine-preventable diseases and vaccines, specifically on these five topics:

I this column, please find links to background material.

Contents

1. Vaccine-preventable diseases

The number of diseases that may be fully or partially prevented by vaccines is steadily increasing. In most EU-countries, ten diseases are targeted in national childhood vaccination programmes. Usually, these ten diseases are covered by three vaccine products, in one or more doses.

Covered in most EU-countries

- Diphtheria
- Tetanus
- Pertussis
- Poliomyelitis
- Hib-disease
- Hepatitis B
- Pneumococcal disease
- Measles
- Mumps
- Rubella

Covered in some EU-countries

- Rotavirus gastroenteritis
- Tuberculosis
- HPV infection
- Meningococcal disease
- Influenza
- Hepatitis A
- Varicella

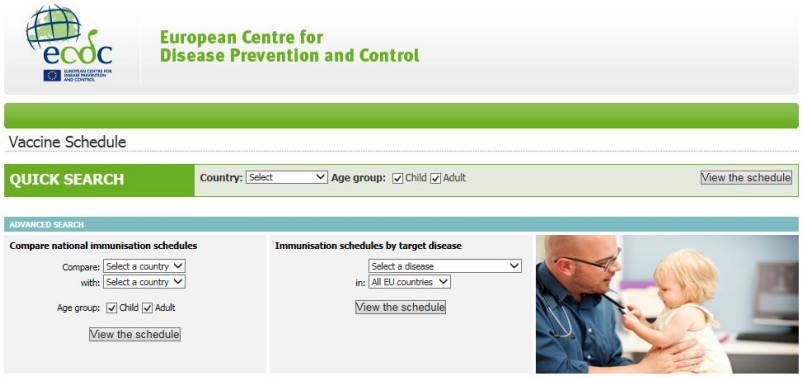
Other diseases

- Rabies
- Yellow fever
- Japanese encephalitis
- Cholera
- Tick-borne encephalitis
- Malaria

Some diseases are targeted by the vaccination programme of only some EU countries. And vaccines against yet other diseases are used for special groups only, among them mainly travellers.

The European Centre for Disease Prevention and Control (ECDC) maintains a public database of vaccination schedules in EU countries:

ECDC Vaccine Scheduler: http://ecdc.europa.eu/en/eurovaccine

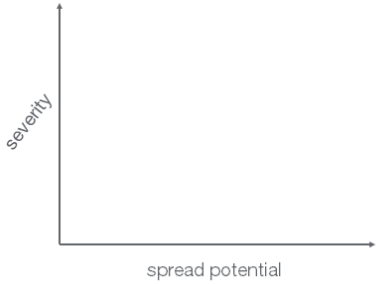


This is a very useful tool for studying the programme in individual countries, or for looking across EU on the variation in schedules for certain (or most!) vaccines. For instance, hardly any two countries have the same schedule for measles vaccination.

2. Burden of infectious diseases

The burden of an infectious disease is a measure of the population ill health (deaths and disability) resulting from the disease. Thus, we need to look at both **severity** of disease (measured by e.g. case-fatality risk or disability risk) and the potential for spread of the disease, which determines the number of affected people.

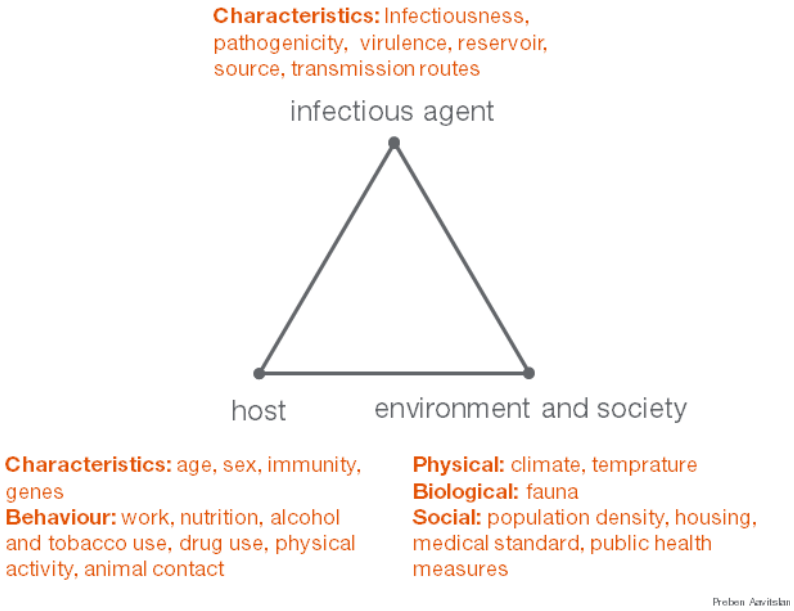
WHO on the use of Disability-Adjusted Life Year (DALY) to quantify the burden of disease from mortality and morbidity http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/



These two factors are independent. The product of them can be seen as the disease burden.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) http://www.healthdata.org/gbd

Both the severity and the spread potential are determined by features of the infectious agent, the infected host or the environment and society. In the figure below, these features are listed.

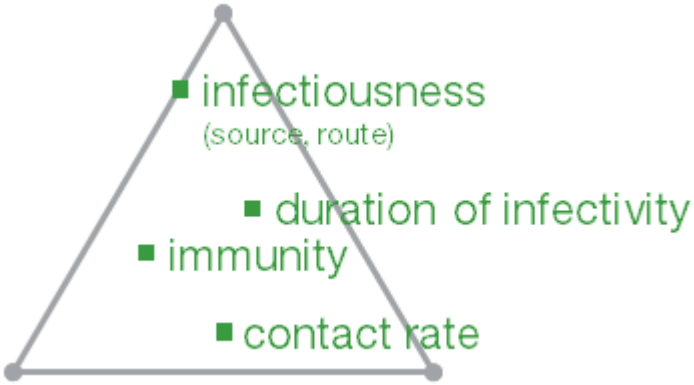


For instance, the **severity** is mainly determined by the virulence of the agent, the immunity of the host (which may ameliorate, if not fully prevent, a disease), the quality of treatment, and the underlying diseases, nutritional status and age of the host.

The **spread potential** is mainly determined by the infectiousness of the agent (and its source and route of transmission), the duration of infectivity of the host, the contact rate between the infected host and other individuals, and the susceptibility of those individuals.

The product of these four factors equals the reproduction number R of an infectious disease in a given situation. R is the number of secondary cases produced by an average infected

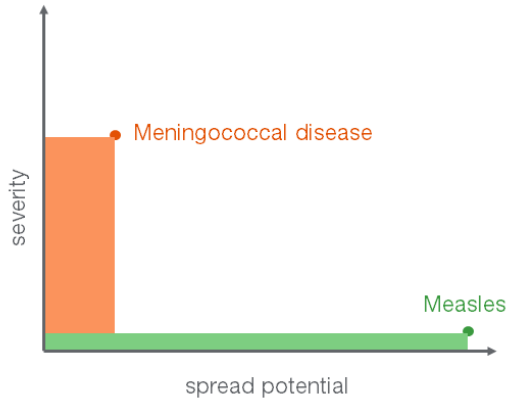
host.



This product can be written like R = pcds:

R =	p	c	d	s
Factor	Infectiousness of agent	Contact rate	Duration of infectivity	Proportion susceptible
Measures	Hygiene. Personal protective equipment	Isolation of the sick. Quarantine of the suspects. Acticity restrictions.	Treatment that kills agent.	Vaccination

We now see that vaccine-preventable diseases may vary along both the severity and the spread potential axis. Take for instance meningococcal disease: It is very severe, with a case-fatality risk of 10-20 %. Its spread potential, however, is low (except for some epidemics in the African «meningitis belt»). Most cases are solitary. Still, the high severity produces a rather high disease burden (read area in the figure).



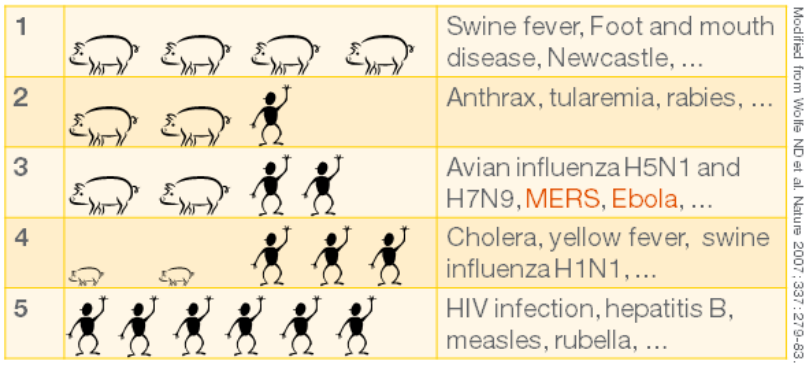
Measles, on the other hand, has a low case-fatality risk in Europe; perhaps 0.02%. Its spread potential, however, is very large. The measles virus spreads by airborne transmission. In a population of only susceptible individuals, an index case will on average infect around 15 people. (We say that the *basic* reproduction number - R_0 - is 15.) In the case of measles, then, it is the high spread potential - not the severity - that causes the high disease burden (green area in figure).

One major problem with using only disease burden to prioritise preventive resources among infectious diseases is that we then

only consider diseases that we know and that have a measurable disease burden. The last few years have, however, taught us that diseases may emerge to rapidly cause heavy disease burdens. Ebola viral disease, MERS and Nipah viral disease are just a few examples. Usually, these new diseases emerge in humans from an animal reservoir, which is not surprising. Vertebrates share many diseases, and the closer two species are (in phylogenetical terms); the more likely they are to share infectious agents.

Wolfe and co-workers have proposed a development two several stages:

At the first stage there are agents that are present in only one or a few animal species.



Modified from Wolfe ND et al. Nature 2007; 337: 279-83.

At the second stage, we find infectious agents that occasionally manage to jump from their animal hosts to infect humans, but the agents are not adapted to humans and the spread stops. Humans are a dead end; the reproduction number among humans is zero. Examples of such diseases include anthrax, tularaemia, rabies, and borreliosis.

Factors that increase the risk of spread from animals to humans are the density of animals, the prevalence of infection among them, the rate of contact between animals and humans, and the infectiousness of this contact. Characteristics of the infectious agent and a large phylogenetic distance between the animal in question and humans may reduce the likelihood of interspecies spread.

In this way, argues Wolfe, do we understand why some animals more than others have been important sources of new zoonoses. Rats have been important because we come so much in contact with them. Chimpanzees have been important because they are so similar to us. Elephants and polar bears, on the other hand, are less likely sources because we tend to avoid close contact with them (at least with the polar bears!) and they are not so similar to us.

In the third stage, we find infectious agents that have their main reservoir among animals, and that rarely infect humans and set

«The burden of disease is a less useful measure to set public health priorities for infectious diseases as compared with non-communicable diseases. Ministers of health and key policymakers should not be lulled into thinking that the best use of resources is to allocate them only to the most obvious current problems. The biggest public health impact against an infectious disease is often when the numbers are small. Good public health sense would suggest that ignoring many of the emerging zoonotic diseases today because they exhibit a low burden of disease may result in catastrophic problems tomorrow.»
Berkelman R, LeDuc J. **How useful is 'burden of disease' to set public health priorities for infectious diseases?** J Public Health Policy 2015; 36: 283–6.

Wolfe ND, Dunavan CP, Diamond J. **Origins of major human infectious diseases.** Nature 2007; 447: 279-83.

off chains of interhuman transmission. The reproduction number, however, is less than 1, so the epidemics sooner or later stop by themselves. The disease cannot be sustained among humans; rather it requires an animal reservoir.

Avian influenza H5N1 and H7N9 and MERS certainly are at this stage. We used to classify also Ebola virus disease here, but the recent outbreak in West Africa indicates that Ebola virus may be close to a stage 4 pathogen.

At the fourth stage, we find infectious agents that once came from animals, but since have adapted to humans. Over time, humans have replaced animals as the main source of new cases. Cholera, yellow fever and swine influenza H1N1 are examples. When swine influenza H1N1 emerged among humans in 2009, it was already so adapted to humans that infections from swine to humans had little impact compared to interhuman transmission. (In Norway, one of the few countries with no influenza in swine, one issue during the 2009 pandemic was to avoid spread of swine influenza H1N1 from humans to swine!)

At the fifth stage, we find infectious agents that have adapted to humans so well that they no longer have an animal reservoir. They have become exclusive human pathogens.

The enormous outbreak of Ebola virus disease in West Africa has demonstrated the large disease burden caused by an emerging disease. No-one could have foreseen this large disease burden, not only from Ebola itself, but also from other diseases that have been neglected while the health services in the affected countries have been desperately fighting Ebola. Thousands of children orphaned by Ebola are a huge extra burden.

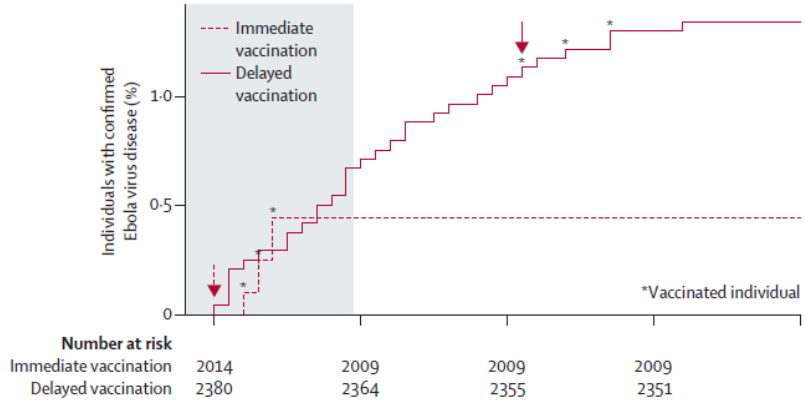
More on Ebola:
http://epidemi.no/?page_id=1158

Fortunately, several candidate Ebola vaccines had been developed and were almost ready for clinical testing when the

WHO on Ebola vaccines:
http://who.int/medicines/ebola-treatment/emp_ebola_vaccines/en/

outbreak took off in West Africa. One product, a Canadian-developed, recombinant, replication-competent vesicular stomatitis virus-based candidate vaccine expressing the glycoprotein of a Zaire Ebolavirus (rVSV-ZEBOV), was tested in a phase III trial in Guinea, using a is a novel cluster-randomised trial design – called ring vaccination trial – to assess vaccine efficacy and effectiveness during outbreaks. Around each new case, contacts and contacts of contacts were immediately identified and offered vaccine. By randomisation, vaccination was given immediately in some rings and three weeks later in other rings. The key finding, indicating a very high efficacy, was that there were no Ebola cases in the immediately vaccinated rings (after the ten-day period for gaining immunity post vaccination), see figure.

Henao-Restrepo AM, et al. **Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial.** Lancet 2015; 386: 857-66.



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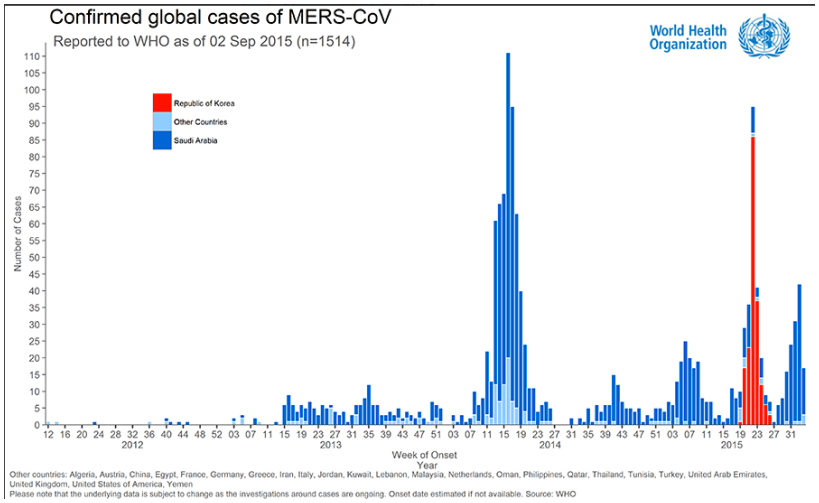
For MERS, there is still no vaccine, neither for humans, nor for dromedaries, who are believed to be the main source (if not reservoir) for human infections. The international outbreak with an epicentre in Saudi-Arabia has lasted since 2012 and has already sickened at least 1500 people and killed some 500. The lack of a vaccine points to deficiencies in the international system for rapidly bringing vaccines for new diseases to the market.

More on MERS:
http://epidemi.no/?page_id=566



Thus, in summary, the estimation of disease burden is useful

when considering introduction of vaccines against established diseases, but less useful when it comes to newly emerging diseases.

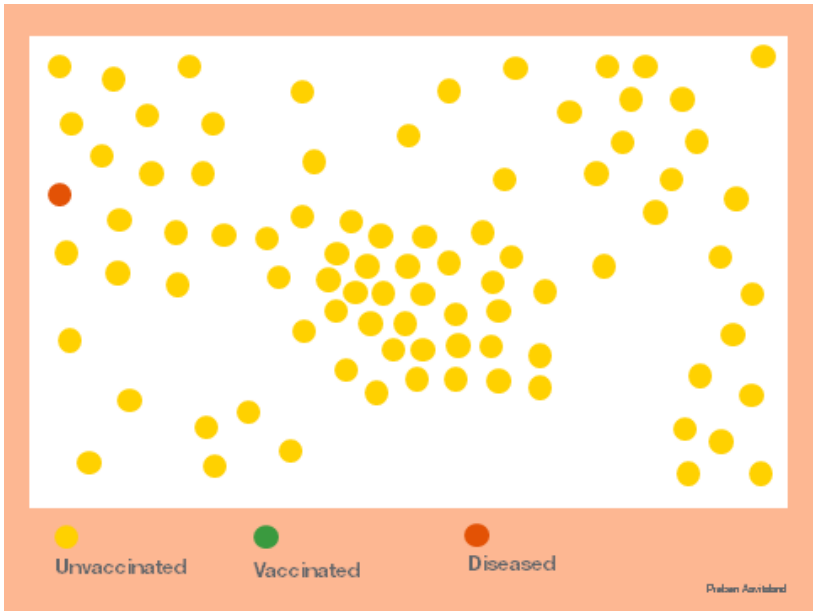
Only disease burden?

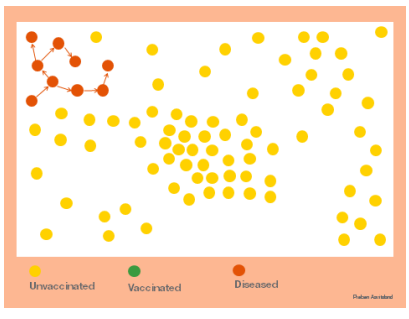
- Current burden of a new disease is ≈zero
- Ignoring today → catastrophe tomorrow?
- Preparedness for the unpredictable
- Challenge of financing

3. Community immunity

We usually think of vaccines as protecting individuals. They do, but many vaccines in many populations will also protect communities – including unvaccinated people – by reducing transmission. When there are many immune people in the population, the spread potential is greatly reduced. Then, also unvaccinated people may avoid coming into contact with the infectious agent. Epidemics cannot be sustained because there are simply not enough susceptible people.

Fine PEM, Mulholland K. **Community immunity.** In: Plotkin SA, Orenstein WA, Offit PA. Vaccines. 6th ed. Elsevier Saunders, 2013.





In this population of unvaccinated (and thus susceptible) people, an infectious person arrives. This person will infect others, and the disease will propagate until almost all have been infected. Then, the epidemic will die out; there are almost no more

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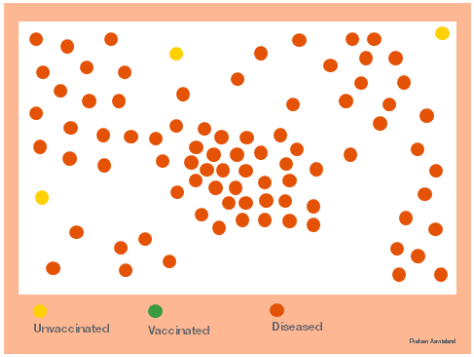
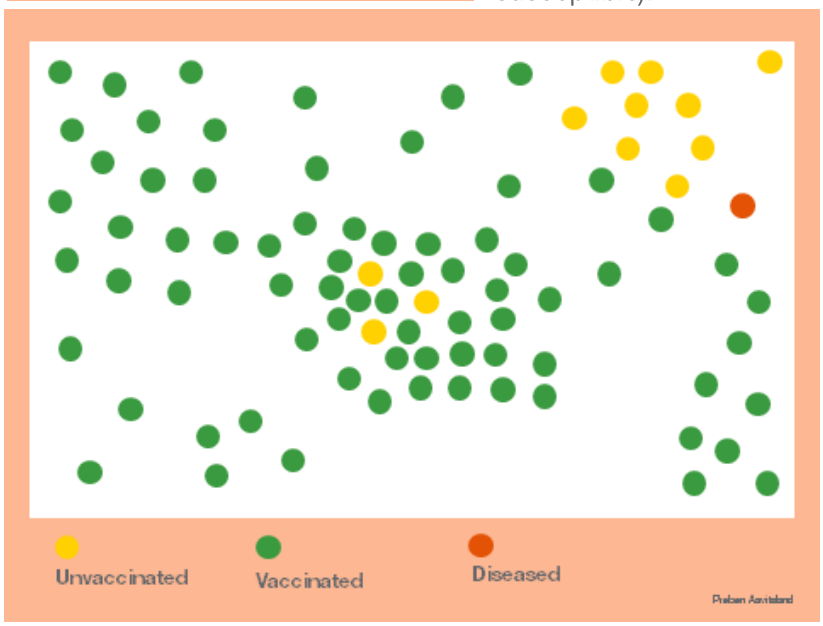
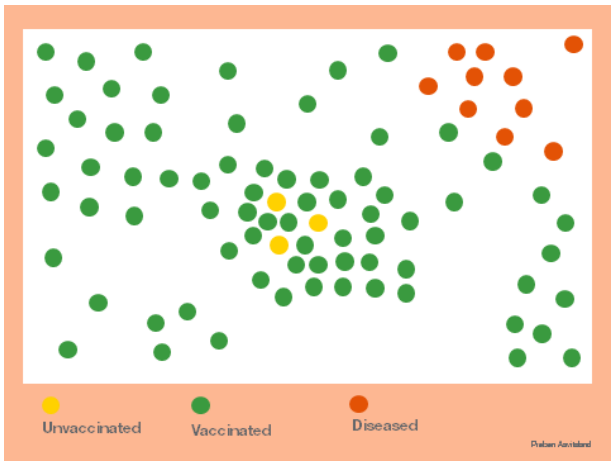


susceptible that the agent can spread to. Some avoid the infection, by luck.

Consider another population where most individuals are vaccinated and immune (non-susceptible):



When an infectious person arrives, the disease may spread to the few unvaccinated individuals who are clustered together (in the top right corner), but those who are scattered around among the vaccinated people will be indirectly protected. This is sometimes referred to as herd immunity; the «herd» of vaccinated people protect the unvaccinated in their midst.



Thus, we can define herd immunity as the indirect protection of nonimmune persons by the presence and proximity of immune persons. By herd immunity, the community protection by vaccination is larger than the sum of individuals' protection.

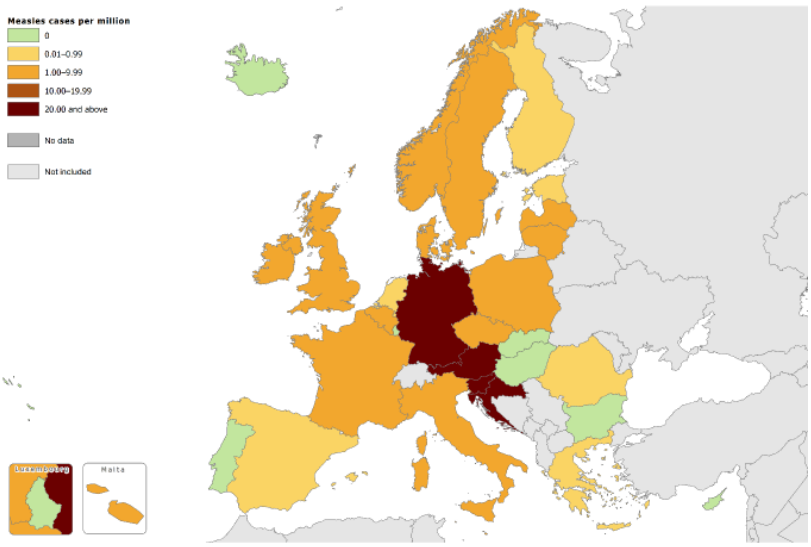
4. Selected news and epidemiological updates

Measles

Measles remain a large problem in the EU, with elimination not in sight. The last year, some 4000 cases have been registered. This is probably an underestimate. ECDC's map shows that the problem is largest in Germany, Austria and Croatia. During the last few years, many cases have also been noted France, Italy and the UK.

ECDC's vaccination gateway: http://ecdc.europa.eu/en/eurovaccine/Pages/default.aspx

Figure 3. Measles notification rate (cases per million) by country, July 2014–June 2015, EU/EEA countries (n=4 224)



Note: Notification rate is also calculated for countries that have not reported consistently for the past 12 months.

ECDC. **Measles and rubella monitoring.** July 2015.

Measles is an extremely infectious disease. The only way to stop its spread is by vaccination programmes that leaves at least 95 % of children immune. This has proven very difficult in many EU countries.

Paradoxically, mass media attention on measles this year has centred on an outbreak traced to Disneyland in California. This outbreak had only some 125 cases, much less than the European outbreaks. In California, the outbreak has led to changes in the public health law, ending the «Personal-Belief Exemptions» to vaccination.

Zipprich J. Measles Outbreak — California, December 2014–February 2015. MMWR 2015; 64:;153-4.
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Such measures are not being discussed so much in Europe.

Reasons for non-vaccination

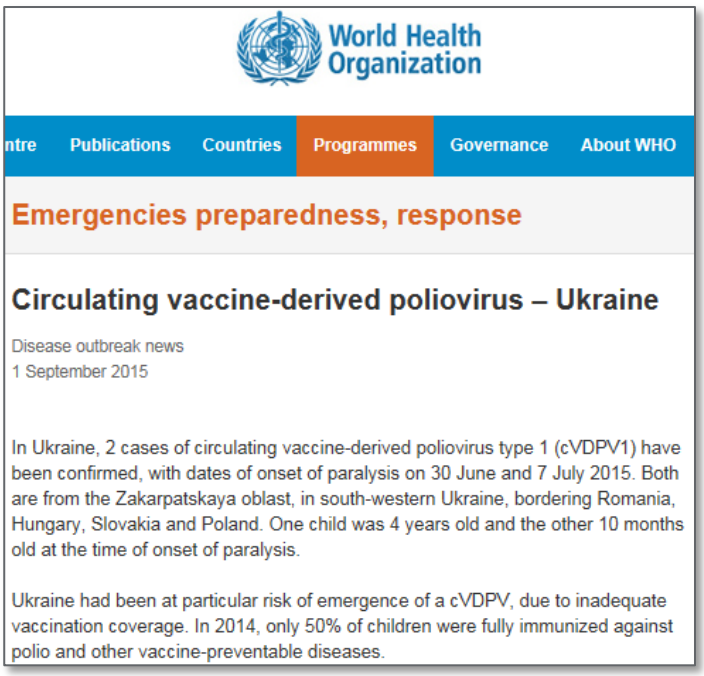
- Vaccine **refusal**: Religious or philosophical objection
- Vaccine **hesitancy**: uncertainty regarding effectiveness and safety
- Real contraindications (very rare)
- False contraindications (common)
- Hard to reach
- Administrative errors

Before contemplating mandatory vaccination, policymakers need to analyse what reasons parents have for not vaccinating their children, and how mandatory vaccination would affect those reasons. In my experience from Norway, the most common reasons for non-vaccination are vaccine hesitancy, false contraindications and administrative errors. I suggest that there are better ways of addressing those reasons than simply mandating vaccination.

Poliomyelitis

This year, there have been only 37 cases of poliomyelitis caused by wild polio virus in only two countries, Pakistan and Afghanistan. These cases occur in regions where islamistic terrorists object to vaccination and murder vaccinators. If these challenges can be overcome, the world will again be on track for eradicating this horrible disease.

Global Polio Eradication Initiative
http://www.polioeradication.org/

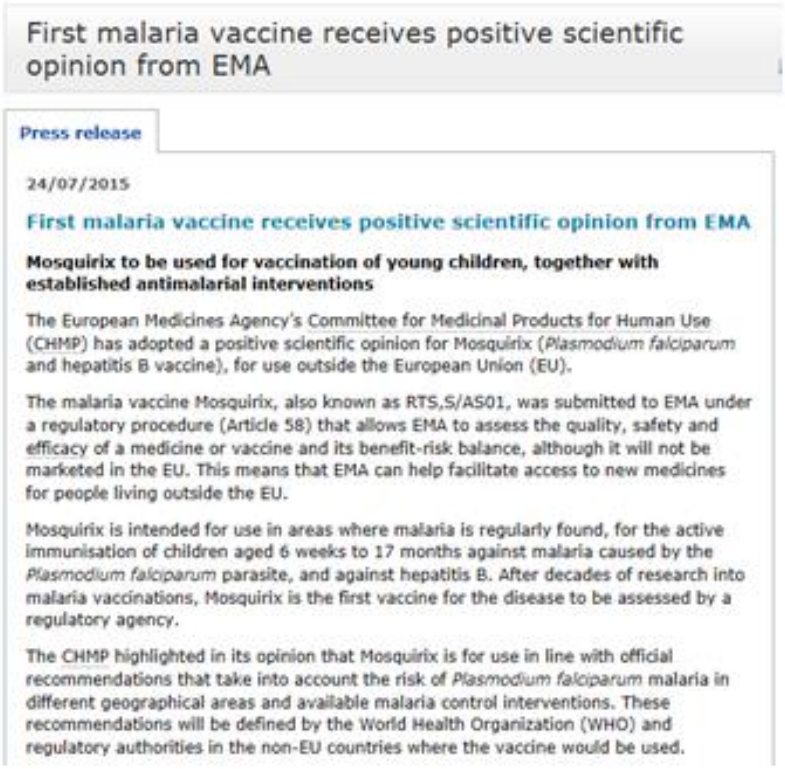


WHO Disease Outbreak News
http://www.who.int/csr/don/01-september-2015-polio/en/

Two days ago, WHO reported two cases of «circulating vaccine-derived poliovirus disease» in Ukraine. This is poliomyelitis caused by poliovirus that originally was the attenuated poliovirus in the oral polio vaccine (OPV). It has been fecally excreted from vaccinees and then silently spread between unvaccinated people and ultimately mutated into a disease-causing virus. This adverse events of the polio vaccination programme can only be prevented by making sure the population is well immunised.

Malaria

A month ago, for the first time a malaria vaccine received a positive scientific opinion from the EMA. It combines vaccination against malaria (caused by *P falciparum*) and hepatitis B. The vaccine provides children good, but far from perfect, protection against malaria.



First malaria vaccine receives positive scientific opinion from EMA

Press release

24/07/2015

First malaria vaccine receives positive scientific opinion from EMA

Mosquirix to be used for vaccination of young children, together with established antimalarial interventions

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a positive scientific opinion for Mosquirix (*Plasmodium falciparum* and hepatitis B vaccine), for use outside the European Union (EU).

The malaria vaccine Mosquirix, also known as RTS,S/AS01, was submitted to EMA under a regulatory procedure (Article 58) that allows EMA to assess the quality, safety and efficacy of a medicine or vaccine and its benefit-risk balance, although it will not be marketed in the EU. This means that EMA can help facilitate access to new medicines for people living outside the EU.

Mosquirix is intended for use in areas where malaria is regularly found, for the active immunisation of children aged 6 weeks to 17 months against malaria caused by the *Plasmodium falciparum* parasite, and against hepatitis B. After decades of research into malaria vaccinations, Mosquirix is the first vaccine for the disease to be assessed by a regulatory agency.

The CHMP highlighted in its opinion that Mosquirix is for use in line with official recommendations that take into account the risk of *Plasmodium falciparum* malaria in different geographical areas and available malaria control interventions. These recommendations will be defined by the World Health Organization (WHO) and regulatory authorities in the non-EU countries where the vaccine would be used.

WHO will no consider what role the vaccine will have in the combination with other measures to combat malaria in highly endemic countries.

RTS,S Clinical Trials Partnership. **Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial.** Lancet 2015; 386: 31-45.

A wish list…

- Improved tuberculosis vaccine
- Improved malaria vaccine
- HIV vaccine
- Hepatitis C vaccine
- Universal influenza vaccine
- Vaccinces against enteric infections
- MERS vaccine
- More rapid development and testing of vaccines

A vaccine against malaria has long been on the wish list of public health practitioners. This list also contains vaccines against HIV-infection, tuberculosis, hepatitis C and enteric infections as well as a universal influenza vaccine.

5. Criteria for introducing vaccines in vaccination programmes

As vaccination programmes in Europe are usually paid for by the governments, it is only natural that governments decide on the contents of the programmes. In most countries, a national vaccination committee advises the government. Consumer

involvement is becoming increasingly common. For reasons of transparency, accountability and trust, explicit criteria for introducing vaccines have been introduced in several countries. These criteria usually centres around disease burden, effectiveness and safety of vaccination, and costs, as in The Netherlands:

Houweling H et al. **Criteria for inclusion of vaccinations in public programmes.** Vaccine 2010; 28: 2924–31.

Seriousness and extent of the disease burden

1. The infectious disease causes **considerable disease burden** within the population.
    - The infectious disease is serious for individuals, and
    - The infectious disease affects or has the potential to affect a large number of people.

Effectiveness and safety of the vaccination

2. Vaccination may be expected to considerably **reduce the disease burden** within the population.
    - The vaccine is effective for the prevention of disease or the reduction of symptoms.
    - The necessary vaccination rate is attainable (if eradication/elimination or the creation of herd immunity is sought).
3. Any **adverse effects** associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4. The **inconvenience** or discomfort that an individual may be expected to experience in connection with his/her **personal vaccination** is **not disproportionate** in relation to the health benefit for the individual concerned and the population as a whole.
5. The **inconvenience** or discomfort that an individual may be expected to experience in connection with the **vaccination programme** as a whole is **not disproportionate** in relation to the health benefit for the individual concerned and the population as a whole.

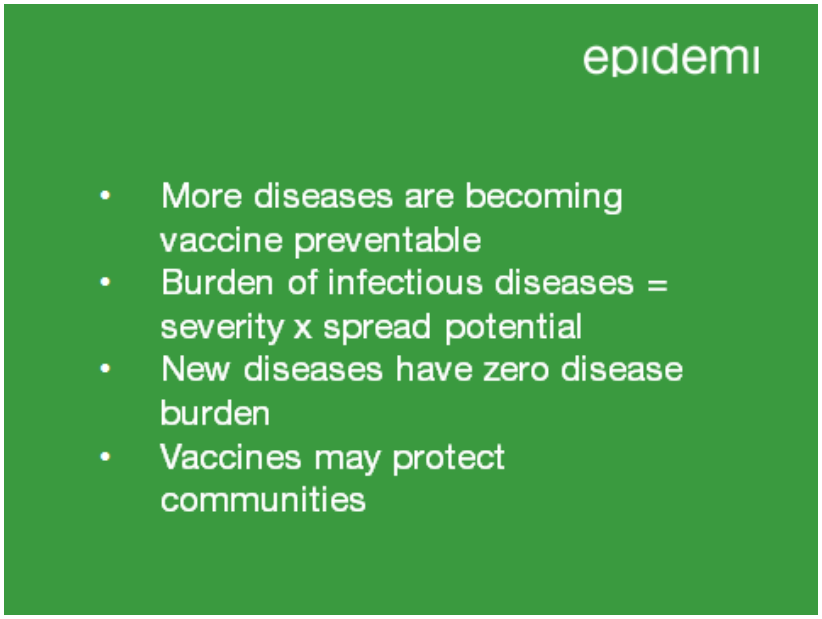
Efficiency of the vaccination

6. The **balance between the cost of vaccination and the associated health benefit** compares favourably to that associated with other means of reducing the relevant disease burden.

Priority of the vaccination

7. **Relative to other vaccinations** that might also be selected for inclusion, provision of this vaccination serves an urgent public health need at reasonable individual and societal costs.

Conclusion



Thank you for your attention!