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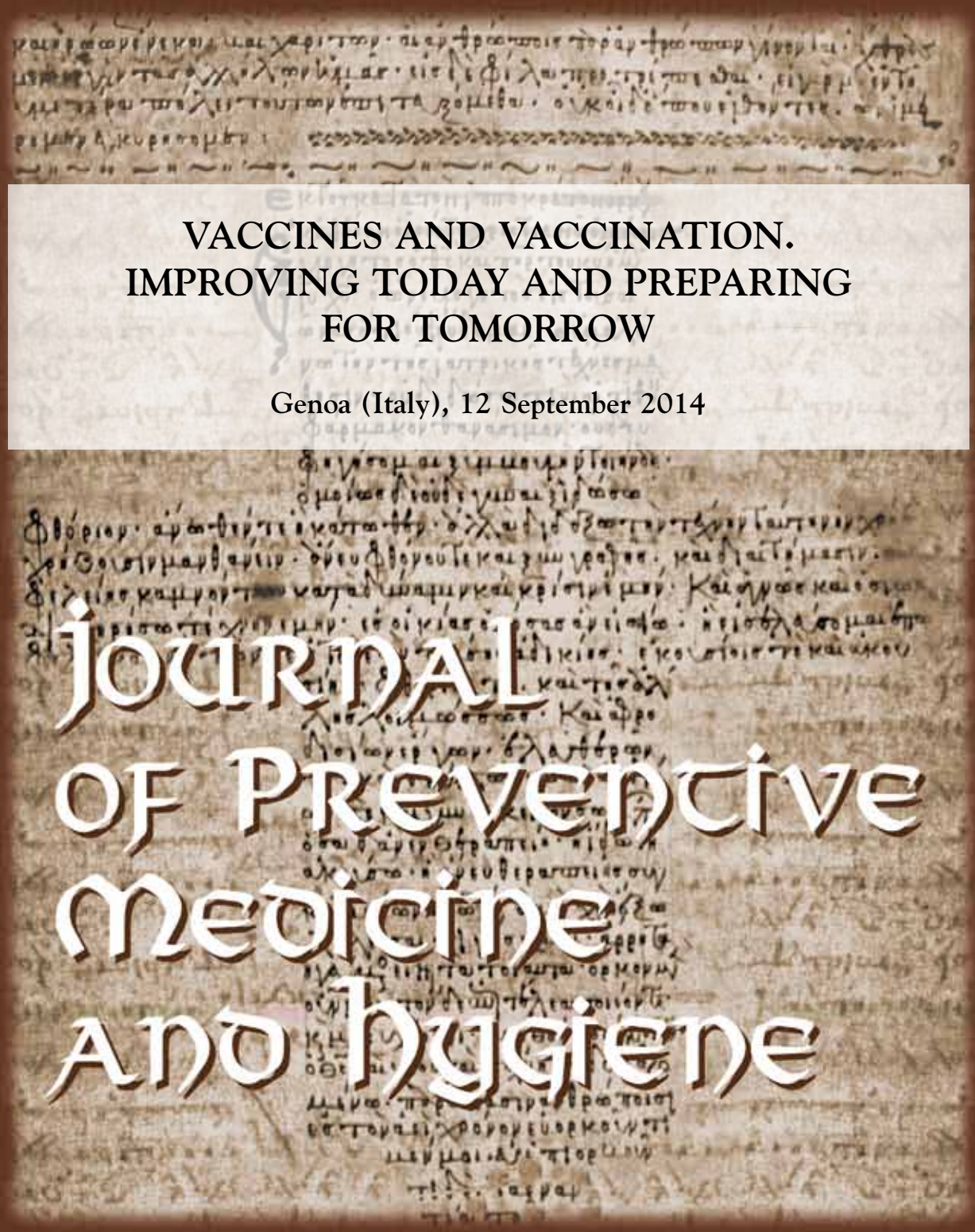
# VACCINES AND VACCINATION. IMPROVING TODAY AND PREPARING FOR TOMORROW

Genoa (Italy), 12 September 2014



# JOURNAL OF PREVENTIVE MEDICINE AND HYGIENE

The original document of Hippocrates' oath

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*Genoa (Italy), 12 September 2014*

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EDITORIAL

# The "urban myth" of the association between neurological disorders and vaccinations

R. GASPARINI, D. PANATTO, P.L. LAI, D. AMICIZIA
Department of Health Sciences, University of Genoa, Italy

Key words

Vaccine • Vaccinations • Neurological disorders

Summary

*In modern society, a potentially serious adverse event attributed to a vaccination is likely to be snapped up by the media, particularly newspapers and television, as it appeals to the emotions of the public. The widespread news of the alleged adverse events of vaccination has helped to create the "urban myth" that vaccines cause serious neurological disorders and has boosted anti-vaccination associations. This speculation is linked to the fact that the true causes of many neurological diseases are largely unknown. The relationship between vaccinations and the onset of serious neuropsychiatric diseases is certainly one of coincidence rather than causality. This claim results from controlled studies that have excluded the association between vaccines and severe neurological diseases, therefore it can be said, with little risk of error, that the association between modern vaccinations and serious neurological disorders is a true "urban myth".*

## Introduction

Many severe neuropsychiatric diseases, such as Alzheimer's disease, multiple sclerosis, autism, epilepsy, schizophrenia, encephalomyelitis, encephalopathies, transverse myelitis and optic neuritis, do not yet have a well-defined etiopathogenesis, although important progress has been made on their causes. Several studies have shown that these diseases are due both to genetic factors (intrinsic factors) and environmental factors (extrinsic factors). With regard to autism spectrum disorders, for example, as early as 1977 Folstein and Rutter published the first study of twins and autism focusing on genetic aspects, which showed that the concordance rate in monozygotic twins was much higher than in fraternal twins [1]. Incomplete understanding of the causes of the above diseases has sometimes led to the belief that they are caused by vaccinations; in reality, however, the relationship between vaccinations and the onset of serious neuropsychiatric diseases is certainly one of coincidence rather than causality. In modern society, a potentially serious adverse event attributed to a vaccination is likely to be snapped up by the media, particularly newspapers and television, as it appeals to the emotions of the public. Indeed, a "good" item of news is one that arouses fear or hope. Thus, for example, considerable attention was devoted to the publication of Andrew Wakefield's article, which linked measles vaccination to pervasive developmental disorders and non-specific colitis [2], and to the case of Heather Whitestone, who was elected Miss America despite her deafness, which had erroneously been attributed to the diphtheria, tetanus and pertussis vaccine [3]. The widespread news of the alleged adverse events of vaccination has helped to create the "urban myth" that vaccines cause serious neurological disorders and has boosted anti-vaccination associations. These associations can be traced back to the nineteenth century, with the foundation of the National Anti-Vaccination League in 1896 in Britain and the Anti-Vaccination Society of America in 1879 in the US [4]. By the end of the twentieth century, opposition to vaccinations had strengthened in most developed countries because diseases preventable by vaccinations had become increasingly rare. Thus, with regard to the subject of vaccinations, the ethical, social, religious and legal issues cannot be ignored.

## Neurological diseases without a well-defined etiopathogenesis

a) *Alzheimer's disease.* Alzheimer's disease (AD) is the most common form of dementia among older people. AD begins slowly, first involving those parts of the brain that control thought, memory and language. People with AD may have trouble remembering things that happened recently or the names of people they know. Over time, the symptoms worsen; sufferers may no longer recognize family members or have difficulty speaking, reading or writing. Subsequently, they may become anxious or aggressive, or wander away from home. Eventually, they need total care [5]. Scientists do not yet fully understand what causes Alzheimer's disease, but it has become increasingly clear that it develops because of a complex series of events that take place in the brain over a long period of time.

It is likely that the causes include some mix of genetic, environmental and lifestyle factors [6].

b) *Autism*. The autism spectrum disorders are developmental disabilities, which debut during childhood. Their clinical presentation is characterized by disorders in social and communication relationships with others and by repetitive, stereotyped behaviors [7]. Although the causes of autism are not yet fully understood, it is certain that genetic factors are involved. However, the genetics of the disorder is extremely complex; indeed, a recent study has shown that at least 127 genes are involved [8]. Moreover, extrinsic causes would act only during pregnancy [9].

c) *Encephalomyelitis*. Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating state, which mainly affects the white substance of the neuraxis. The disease manifests itself as an acute onset encephalopathy combined with multiple neurological deficits, and is typically self-limiting [10-12]. ADEM usually develops after viral or bacterial infection and, in the past, it could develop after vaccination against rabies or smallpox; in some patients, however, the cause remains unknown. Many infectious agents have been linked to ADEM, including chickenpox, mumps, measles, rubella, influenza, coxsackievirus B, herpes simplex virus, *Legionella, Campylobacter, Borrelia burgdorferi, Salmonella typhi, Mycoplasma pneumoniae, Chlamydia pneumoniae,* etc. [13].

d) *Encephalopathies*. The term encephalopathy indicates any widespread disease of the brain that alters the function or structure of the brain. Encephalopathy can be caused by an infectious agent (bacteria, viruses, or prions), by a mitochondrial or metabolic dysfunction, brain tumors or increased pressure in the skull, prolonged exposure to toxic elements (including solvents, drugs, radiation, paints, industrial chemicals and certain metals), chronic trauma, poor nutrition, or lack of oxygen or blood flow to the brain. The hallmark of encephalopathy is an altered mental state. Depending on the type and severity of the encephalopathy, the most common neurological symptoms are progressive memory loss and the deterioration of cognitive abilities, inability to concentrate, lethargy, and the gradual loss of consciousness [14].

e) *Epilepsy*. Epilepsy is a disorder of the central nervous system in which the activity of nerve cells in the brain is interrupted, causing seizures or periods of unusual behavior, strange sensations and sometimes loss of consciousness. Symptoms may include confusion, temporary absence and involuntary movements of the arms and legs. These symptoms may be associated to psychological symptoms. In about half of cases, epilepsy does not have an identifiable cause; in the other half, the condition can be attributed to various factors. The genetic influence seems to be very important. Indeed, some researchers have estimated that in 70% of cases there is a genetic influence, and that more than 500 genes may be linked to the condition [15]. Head trauma, brain tumors, stroke and some infectious diseases, such as AIDS, can cause epilepsy. Even prenatal injury, caused by an infection in the mother, malnutrition or oxygen deficiency, for example, may be involved. Epilepsy can sometimes be associated to developmental disorders, such as autism and neurofibromatosis.

f) *Optic neuritis.* Optic neuritis is a condition characterized by inflammation of the optic nerve. While it may be associated to a variety of systemic autoimmune diseases, the most common form is best known for its association to multiple sclerosis [16]. Recurrence of optic neuritis after a single, isolated incident is not uncommon [17]. Patients report sub-acute visual loss and difficulty in seeing colors, especially red, which appears faded. Pain on eye movement is often present. Visual loss is usually monocular, but may involve both eyes, and generally reaches its peak within hours or days. The majority of patients recover their visual acuity.

g) *Schizophrenia.* Schizophrenia is a debilitating mental illness that affects 1% of the population worldwide. Schizophrenia is characterized by positive and negative symptoms. The former include hallucinations and voices that speak to the patient; the latter include loss of the sense of pleasure, loss of will and social isolation [18]. A family history of schizophrenia is the main risk factor [19]. Other hypothetical risk factors include: the season and place of birth, socioeconomic status and maternal infections [20]. Schizophrenia appears to be a polygenic disorder which can be influenced by environmental factors [21].

h) *Transverse myelitis.* Transverse myelitis is a neurological disorder caused by bilateral inflammation of a level, or segment, of the spinal cord. This inflammation damages myelin, disrupting communications between the nerves of the spinal cord and the rest of the body. The symptoms of transverse myelitis include a loss of spinal cord function for several days or weeks. The onset is characterized by a sudden back pain, muscle weakness, or abnormal sensations in the fingers and toes. The disease can rapidly progress, causing more severe symptoms, including paralysis, urinary retention and loss of sphincter control. Although some patients recover and are left with minor damage or no residual problems, others suffer permanent disabilities that affect their capacity to perform normal everyday activities. Researchers are uncertain of the exact causes of transverse myelitis. The inflammation which causes such extensive damage to the nerve fibers of the spinal cord can result from viral infections or abnormal immune reactions. Transverse myelitis may also occur as a complication of syphilis, measles and Lyme disease [22].

## Causality or casualness?

### Alzheimer's disease

An "urban myth" concerning the association between influenza vaccination and Alzheimer's disease was created in 2005 after an episode of the television show "Larry

King Live" in which Bill Maher was being interviewed by Larry King. Maher argued that "if you have a flu shot for more than five years in a row, there's ten times the likelihood that you'll get Alzheimer's disease" [23]. Dr. Maher was referring to Dr. Hugh Fudenberg's speech during the 1st annual International Public Conference on Vaccination, held by the National Vaccine Information Center in Arlington, Virginia in 1997 [24]. However, a study conducted by Verreault et al. in 2001 refuted Maher's claim. Indeed, by means of a prospective study – the "Canadian Study on Health and Aging", a cohort Study on dementia – Verreault et al. had shown that increased exposure to vaccines against diphtheria, tetanus, polio and flu not only was not a risk of contracting Alzheimer's, but could actually protect against the disease [25].

### Autism

Regarding Mumps/Measles/Rubella (MMR) vaccines, the *British Medical Journal* [26] defined the main study that linked these vaccines to autism as a "deliberate fraud". This conclusion resulted from an investigation conducted by the investigative journalist Brian Deer into the research originally published in 1998 by the journal the Lancet, before being withdrawn in February 2010 [2]. The paper had associated the administration of MMR vaccine with a new syndrome characterized by autism and ileal lymphoid hyperplasia associated to non-specific colitis. According to Fiona Godlee, the editor in chief of the BMJ, the article by Wakefield "was based not on bad science but on a deliberate fraud" [26]. In her editorial, published in 2011, Godlee pointed out that in Wakefield's research:

- only one of the nine children who allegedly had autism really did;
- five of the children had developmental difficulties before vaccination, although the article claimed that all were in good health before vaccination.
- Although the paper claimed that a mean time of 6.3 days elapsed between vaccination and the onset of symptoms, some children who had their first symptoms months after vaccination. Furthermore, many studies carried out after the publication of the paper by Wakefield et al. demonstrated without any doubt that MMR vaccines do not engender a higher risk of autism or colitis [27-30]. The US Institute of Medicine (IOM) also concluded that "The evidence favors rejection of a causal relationship between MMR vaccine and autism" [31].

### Acute Disseminated Encephalomyelitis (ADEM), Encephalitis and Encephalopathies

With regard to encephalitis, it is necessary to distinguish between acute disseminated encephalomyelitis (ADEM), encephalitis and encephalopathy. Some neurology texts state that ADEM may be caused by vaccines. Actually, this association is linked mainly to the fact that the old vaccines against rabies, which were derived from animal nerve tissue (NTV), namely Fermi and Semple vaccines, could lead to sensitization, not least because of the high number of doses required for post-exposure prophylaxis. However, these vaccines have not been used in industrialized countries since the 1970s, and the World Health Organization (WHO) effectively banned them in 1992. The incidence of neurological Serious Adverse Events (SAE) after administration of rabies NTV varied widely: from 1 per 230 to 1 per 6,000 vaccinations [32]. In the case of smallpox vaccines, too, post-vaccination encephalopathies and encephalitis were well-known, albeit very rare, adverse events (about 1 case per 665,000 vaccinees in the US and 1 case per 345,000 in Italy) [33]. However, as smallpox has been eradicated, smallpox vaccines are no longer used. Subsequently, neurological SAE were attributed to several vaccines, namely: MMR, varicella, influenza, hepatitis A and B, papillomavirus, diphtheria-tetanus-pertussis and menC conjugate vaccines. Regarding the hypothesis that MMR vaccine causes a risk of encephalitis, Duclos et al. estimated an incidence of 1 case per million recipients [34], and studies conducted in Albania [35], Finland [36], the US [37], Great Britain and Ireland [38] suggested that there was no link between MMR vaccine and encephalitis. Indeed, in 2011 the Institute of Medicine concluded that "The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and encephalitis" [31].
In addition, adverse events such as encephalitis and encephalopathy have been reported after the administration of influenza vaccines. Although there are reports (case reports) of encephalitis or encephalopathy after the administration of flu vaccines [39, 40], the controlled studies reported in the literature do not demonstrate a causal association with either inactivated vaccines (TIV) or live attenuated vaccines [41-43]. In this regard, Lee et al. conducted a study on the safety of both the monovalent pandemic vaccine containing the virus H1n1pdm09 and the seasonal vaccine administered separately in the 2009-10 flu season. Having investigated over 1,345,663 individuals who had received the monovalent inactivated pandemic vaccine; 267,715 individuals who had been vaccinated with the live attenuated pandemic vaccine; 2,741,150 subjects vaccinated with the seasonal inactivated vaccine, and 157,838 recipients of the seasonal live attenuated vaccine, the authors found non-significant associations between the vaccines and Guillain-Barré syndrome and other major neurological diseases [44].
With regard to the possible association between the vaccine against hepatitis B and encephalitis or encephalopathy, after analyzing the literature the IOM concluded that, from the epidemiological standpoint, there was no evidence of a possible causal association [45, 46].
As for the hypothetical association between encephalitis / encephalopathy and the Tdap vaccine, the only two controlled studies considered by the IOM reached conflicting conclusions, but both displayed methodological limitations. Moreover, a study conducted in Italy by Greco et al. [47] was refuted by later research [48]. In addition, a study conducted by Yih et al. [49] on 660,000 patients, within the network of the Vaccine Safety Datalink, found a lower risk of encephalopathy (0.84) in patients who received the Tdap vaccine than in the control group. Another study by Ray et al. found a lack of evi-

dence of an association between Tdap vaccine or MMR vaccine and encephalitis or encephalopathy [50].
It has also been speculated that the conjugate vaccine against meningitis C could cause encephalitis or encephalopathy. However, a controlled study conducted by Ward et al. [51] found no causal association between this vaccine and any type of encephalopathy. Safety indications, which also exclude associations between the meningococcal tetravalent conjugate vaccine and encephalopathies, were suggested by large studies [52-54].
In 2000, Creutzfeld Jacobs Disease (CJD), a progressive degenerative disease of the central nervous system, was diagnosed in 73 subjects in England. This disease is caused by infectious proteins, called prions, and can be acquired by consuming the meat of animals affected by "mad cow disease". Since small amounts of bovine serum and gelatin were used to prepare the vaccines obtained from cell culture, it was erroneously assumed that these vaccines were capable of transmitting CJD. However, the probability that the vaccines contained prions was, in fact, nil. Indeed, prions have never been found in the serum or connective tissue of cattle with bovine spongiform encephalopathy (BSE); bovine serum is present in low concentrations in the cell cultures used to prepare vaccines; prions do not multiply in cell cultures *in vitro* and, finally, CJD is transmitted to humans only by eating meat contaminated with prions [32].

### Multiple sclerosis

In 1991, an article by Herroelen et al. [55] published in the Lancet reported the onset of multiple sclerosis six weeks after the administration of DNA-recombinant vaccine against hepatitis B. Although subsequent studies found no association between the vaccine and multiple sclerosis [56], the report aroused considerable mistrust of this vaccine in France, where vaccination coverage (86%) at the age of 6 months is still insufficient [57]. By contrast, in Italy, where vaccination is mandatory for all new-borns, coverage with 3 doses at 24 months stands at 95.3% [58].

### Epilepsy

In 1974, Kulenkampff et al. published a study on an uncontrolled case series which reported mental retardation and epilepsy in children who had received the whole-cell whooping cough vaccine [59]. This study was widely publicized by the mass media, resulting in widespread mistrust of the pertussis vaccine in Britain; subsequently, coverage fell drastically from 83% to 31%. As a result, more than 100,000 cases of pertussis and 36 avoidable deaths occurred in Britain [60]. Similarly, decreased immunization rates and increased deaths due to pertussis were also seen in Japan, where pertussis vaccination was temporarily suspended. In this country, the proportion of children immunized dropped from 70% to 20%, while cases of pertussis increased from 393 (0 deaths) in 1974 to 13,000 (41 deaths) in 1979 [61]. Subsequently, excellent well-controlled studies demonstrated that there was no difference in the rates of mental retardation and epilepsy between children who had been vaccinated against pertussis and those who had not [45, 62].
As for the hypothesis that vaccinations, or some of them at least, may be increase the risk of epilepsy, it should be pointed out that only the vaccine against MMR induces a statistically significant increased risk of febrile seizures [63, 64]. With regard to varicella, hepatitis, diphtheria, tetanus and pertussis, there is no evidence of a correlation between vaccines and febrile seizures [31]. Moreover, the literature suggests that there is no epidemiological evidence of an association between flu vaccines and febrile seizures [41, 42, 65]. However, the risk of febrile seizures is not associated with a major risk of epilepsy [31]. As for the association between MMR vaccines and afebrile seizures, there is evidence of a null association [31].
The hypothesis of a potential link between MMR vaccine and epilepsy was investigated in 2004 by Vestergarden et al. [66], who considered a sample of 439,251 Danish children. They concluded that there was no evidence of an increased risk of epilepsy in children vaccinated with MMR, since their study, which had involved a large sample of subjects, did not find any different in the incidence of epilepsy between vaccinated and unvaccinated children. Furthermore, next-generation sequencing technologies have markedly increased the speed of gene discovery in monogenic epilepsies, allowing us to recognize a genetic cause of the disease in a growing number of patients and improving our understanding of its underlying pathophysiology [67].
Advances in the field of genetics have revealed how misguided it is to attribute serious neurological adverse events to vaccinations. In this perspective, Reyes et al. published a very enlightening article entitled: "Alleged cases of vaccine encephalopathy re-diagnosed years later as Dravet Syndrome". In this paper, the authors reported that, in five subjects with encephalopathy previously attributed to the pertussis vaccine, subsequent genetic investigations revealed Dravet's syndrome, a rare epileptic encephalopathy known to be linked to mutations in the SCN1A (neuronal sodium channel alpha1 subunit) [68].

### Optic neuritis

- MMR, influenza, hepatitis B and DTap vaccines have been suspected of involvement in optic neuritis. With regard to the association of MMR vaccination with optic neuritis, only one paper on a controlled study has been published [69]. In this study, the authors compared 108 cases from three HMOs participating in the VSD (Vaccine Safety datalink) with 228 controls. The conclusion was that MMR vaccination did not increase the risk of optic neuritis. Having examined this study and also considering its limitations, the IOM concluded that: "The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and optic neuritis" [31]. Regarding influenza vaccination and optic neuritis risk, several papers have reported single cases of the disorder after vaccine administration [70-74]. Howev-

er, while case-reports must be regarded as an alarm signal, they do not scientifically demonstrate a correlation. The IOM also evaluated 2 controlled studies [69, 75]; these did not reveal a higher risk among recipients of influenza vaccine than among controls. However, after considering the limitations of these studies, the IOM concluded that: "The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and optic neuritis" [31]. Furthermore, a survey carried out in China after the administration of 89.6 million doses of influenza A H1N1pdm09 vaccine during September 2009 and March 2010 recorded only 3 cases of optic neuritis; the corresponding morbidity rate was 0.003 cases per 100,000 inhabitants, while the morbidity of optic neuritis in Singapore in 2009 was 0.89 per 100,000 people [76]. In addition, no cases of optic neuritis were reported to the US passive surveillance system (VAERS) in the period 2009-10 [77].

- Concerning the risk of optic neuritis in adults after the administration of hepatitis B vaccine, the literature reports two controlled studies: one by DeStefano [69] and one by Payne [75]. The conclusions of both studies were that hepatitis B vaccination did not appear to be associated with an increased risk of optic neuritis in adults. Regarding mechanistic evidence, several case-report studies are available in the literature; for the most part, however, these provided only temporal evidence [78-80].
- A study conducted by Roussat et al. in children found that a presumed trigger for optic neuritis could be suspected in 7 of the 20 children studied: five viral infections and two recent administrations of recombinant hepatitis B vaccine. However, the authors concluded that it was very difficult to establish a causal association between the vaccinations and optic neuritis in infants [81]. With regard to the hypothesized association between optic neuritis and vaccines containing diphtheria and tetanus toxoids or antigens of *Bordetella pertussis*, in 2011 the IOM concluded, on the basis of a single controlled study [69] and a single case report [82], that: "The evidence was inadequate to accept or reject a causal relationship between diphtheria and tetanus toxoid-, or acellular pertussis-containing vaccine and optic neuritis" [31].

#### Schizophrenia

On the relationship between vaccines and schizophrenia, some scholars have speculated that vaccines administered during pregnancy may pose a risk for the unborn child. Although no epidemiological studies have shown the existence of a causal link, some authors, such as Russell Blaylock, have described a theoretical risk. He claims that immune cytokines (IL-1, IL-2, Il-8, IL-6 and TNF-alpha) can cause injury to the baby's developing brain, and that excessive immune stimulation during pregnancy could give rise to autism and other pervasive neurological disorders, including schizophrenia [83-85]. Although experiments on animal models have documented problems of brain development in baby mice born to mothers infected with influenza viruses, this does not demonstrate an association with flu vaccination. Moreover, in a paper entitled "Pregnancy, Immunity, Schizophrenia and Autism", Patterson underlines the fact that cytokines are not the only possible bridge from a mother's infection to the developing fetal brain; indeed, during infections, changes occur in other soluble immunological substances, such as corticosteroids for instance. Furthermore, Patterson highlights the need to consider genetic components and how they act to modulate brain development [86]. In addition, Short et al. have demonstrated that babies born to rhesus monkeys infected with the flu virus during pregnancy have both significantly smaller brains than normal and other brain abnormalities seen in schizophrenia [87]. These results are consistent with the findings of Mednick et al. [88], who reported an increased risk of schizophrenia in persons who had been in the fetal stage in 1957 – the time of the pandemic known as the "Asian" pandemic – and with the study by Byrne et al. [89]. Vaccination should therefore be considered a valuable tool, particularly during pregnancy, in that it may also help to prevent schizophrenia. Indeed, the CDC recommends influenza vaccination in any period of gestation [90].

#### Transverse myelitis

Concerning transverse myelitis, a number of papers have reported the occurrence of this severe adverse event after the administration of different types of vaccines (against measles, varicella, influenza, hepatitis, etc.) [91-97]. However, these are only case reports which do not establish a causal link, as pointed out by the IOM with regard to vaccines against: MR / MMR, chickenpox, influenza, hepatitis A, hepatitis B, papillomavirus, diphtheria, tetanus, pertussis, and meningococcus [31].

## Discussion

Since the 1970s, fears concerning vaccinations have periodically flared among populations. These fears have arisen from reports of individual cases of adverse events or from studies on groups of patients suffering from serious diseases, such as autism, mental retardation, epilepsy, etc.

In truth, vaccinations may elicit serious adverse reactions, such as anaphylactic shock, which is actually a very rare occurrence [98]. However, each vaccination centre must be appropriately equipped to treat this type of event promptly. It cannot be denied that the old vaccines against rabies and smallpox and the oral polio vaccine could cause serious, albeit rare, neurological reactions. However, by the early twentieth century enormous progress had been made in terms of the design, development and quality control of vaccines. Thus, in most cases, only mild and transient side effects can now be expected after vaccination. They are scientifically and rationally designed to stimulate the immune system. Indeed, vaccines stimulate a large number of cells to produce a variety of soluble substances, which interact with

each other in a process that enables lymphocytes and antibodies to be activated, produced, balanced and stored). The substances that are produced during the immune-response include compounds that induce the local symptoms (pain, redness and swelling) and general symptoms of inflammation (fever). Inflammation should therefore be regarded merely as the protective attempt of the organism to remove harmful stimuli, and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) to initiate healing [99].

Unfortunately, however, a severe neurological disease may arise simply by chance after the administration of a vaccine. This has prompted speculation that such diseases may actually be caused by the vaccination, not least because the true causes of many neurological diseases are largely unknown. It is understandable that neurological disorders arouse fear. Indeed, they can cause severe disability, seriously impairing the individual's quality of life (dependence on others, inability to carry out intimate personal care, sexual difficulty, memory loss and impaired judgment, prejudice and social stigma, etc.). Such considerations have fuelled anti-vaccination associations, as in the cases of MMR vaccination and autism and influenza vaccination and Alzheimer's disease. On these issues, the mass media have often adopted a somewhat "sensational" stance, which has impacted negatively on public health in general and on the health of children in particular. In reality, it should be borne in mind that the case reports published in the literature have almost always shown only a temporal association between vaccination and neurological events, while controlled studies have either excluded such associations, as in the case of the MMR vaccine and autism, or have been unable to establish a causal link between the vaccine and severe neurological reactions, such as in the case of diphtheria, tetanus and pertussis vaccines and optic neuritis.

In conclusion, we can say, with little risk of error, that the association between modern vaccinations and serious neurological disorders is a true "urban myth".

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■ Correspondence: Roberto Gasparini, Department of Health Sciences, via Pastore 1, 16132 Genoa, Italy - Tel. +39 010 3538527 - Fax +39 010 3538541 - E-mail: gasparini@unige.it

EDITORIAL

# Adult immunization schedule. The general practitioner's perspective and new tools for a better practice

A. SESSA[1], A. ROSSI[1], I. CRICELLI[2]
[1] Italian College of General Practitioners (SIMG, Società Italiana di Medicina Generale), Firenze, Italy; [2] Health Search, Italian College of General Practitioners, Firenze, Italy

Key words

Adult immunization • General practice • Population health management

Summary

*Vaccine-preventable disease significantly contributes to the morbidity and mortality of adults worldwide. The rates of vaccination against influenza, pneumococcal disease and tetanus in adults and in high-risk group of people are far from the optimal coverage as suggested by Minister of Health. General Practitioners (GPs) can contribute to increase immunization in adults and in elderly people because these age groups attend frequently the surgery of their family doctors for reasons related to their chronic diseases. The GPs, on their side, can proactively involve patients through informatics tools that supply lists of specific patients and electronic alerts in patient records.*

## Introduction

Every time we discuss about immunization program in adult and in elderly people, we should consider two important changes that happened in our current society: the increasing ageing of population and a different old age compared with the past. It has been estimated that since 2005 to 2030 world population over 65 will double (from 500 million to 1 billion) [1]. In 2030 elderly people will be 40% of all population and in Italy in the next 10 years elderly people will be the double compared with 0-14 population.

## A different paradigm

Elderly people showed some social and demographic characteristics in the past decades:
- in the end of working life few years remained to live;
- the end or working life coincided with exclusion of every role in social or recreational activities;
- in the most of cases after-work activities were domestic (particularly for women);
- younger generations took care of elderly, usually inside the same home.

Today we are witness to a new paradigm:
- usually a 65 years old person doesn't feel old;
- usually life expectancy at the time of retirement is long;
- most of retired people are included in social and recreational activities;
- elderly people claim quality of life;
- over 80 people are increasing in number and usually they live with comorbidity and they represent a high cost for each health service.

## Epidemiological scenery

Every year, influenza is responsible of 40,000 deaths in Europe, most of them in elderly people and with chronic diseases [2].
Pneumococcal infections and B hepatitis cause about 45,000 deaths in USA [3]. The economic burden to manage these preventable diseases with adult immunization, other than year-of-life lost, is more than 10 billion dollars every year [4]. In spite of availability of effective and safe vaccines for these diseases, they are underused. Which are the reasons to immunize adult people with vaccines? At least one of these issues is a good reason to immunize them:
1. because they didn't have immunization in childhood;
2. because at present time new vaccines are available;
3. because human immune system gets old and acquired immunity can decline;
4. because elderly people and people with chronic diseases have more susceptibility to diseases preventable with vaccines (influenza, pneumococcal pneumonia).

The lists of immunizations for adults and high risks subjects are reported in Tables I and II.

## Immunizations in adults and elderly people

Tetanus, diphteria and pertussis (TdP) immunization is strongly recommended because in Italy the most of cases of tetanus are in adults who didn't receive any other dose after childhood. About pertussis in Italy, as in other countries, the immunization is very spread in childhood population, but the immunity related to vaccine declined in the next 6 years and so young adults, adults and elderly become susceptible to disease another time [5]. We

recommend that every time patients request tetanus immunization or when we suggest tetanus immunization, we can propose the booster with TdP immunization.
Influenza vaccine has been available since 1940s in an injectable, inactivated form. The high degree of antigenic shift and drift in circulating influenza strains leads to the periodic introduction of strains with high susceptibility in the population, resulting in pandemic spread of disease as in 2009. Influenza vaccine is effective and safe to prevent influenza and complications and to decrease related mortality in high-risk group (patients with chronic diseases, older people and those in contact with high-risk persons). Furthermore, it is important to consider that 2014-2015 season quadrivalent influenza vaccine was available to cover incidental mismatching in co-circulating virus B-strains.
All GPs should remember they can combine influenza with pneumococcal vaccine.
*Streptococcus pneumoniae* is a widespread airway transmittable bacterium causing severe diseases as pneumonia and meningitis. Pneumococcal infections can be the complications of other respiratory infections as influenza and they usually occur in wintertime. Everyone can take a pneumococcal disease but over 65 and patients with chronic diseases have higher mortality rate. Overall pneumococcal infections offer the growing rate of antibiotic resistance: immunization is one of the main weapon of prevention against these diseases.
One-third of people that had a previous infection with varicella zoster virus, will develop a clinical herpes zoster. The herpes zoster vaccine is recommended in adults over 60 years and older, regardless of their history of herpes zoster [6].

## Health professional policy commentary

In current competences all General Practitioners (GPs) must integrate in their daily practice the immunization policies of the National Health Service. Regional and Local Health Services organize the mandatory immunization acting in accordance with the National Immunization Plan [7]. These immunizations are mainly addressed to infants. GPs' duty is to orient, counsel and give recommendations on vaccines characterizing and selecting population groups at high-risk.
We can suggest immunization in adults according to age-group (young adult, adult or old people) (Tab I) or according to risk-group (patients with chronic disease, immunocompromised conditions, pregnancy) (Tab. III) or for employment categories (health care professionals and social care professionals) or for lifestyle (international travelers, history of drug abuse or sexual transmit-

**Tab. I.** Vaccination schedule for adults broken down age group.

| | AGE GROUPS | | |
|---|---|---|---|
| **IMMUNIZATION SCHEDULE** | **19-49 years** | **50-64 years** | **> 65 years** |
| Tetanus, diphtheria, pertussis | Booster every ten years | | |
| Measles, rubeola, mumps | One or two doses | One dose | |
| Chickenpox | Two doses | | |
| Influenza | | | One dose every year |
| Polyvalent Pneumococcus | | | One dose |
| Hepatitis A | Two doses | | |
| Hepatitis B | Three doses | | |

■ Recommended when there are other risk factors (chronic disease, occupational, behavior).

**Tab. II.** Adult Immunizations for high-risk groups and categories.

| Vaccine | Pregnancy | Immuno-deficiency, Cancer, steroid therapy | Diabetes, Cardiac Diseases, Pulmonary Diseases, Hepatic Diseases | Asplenic Patients | Chronic Renal Disease | Hiv Infections | Health Care Professional |
|---|---|---|---|---|---|---|---|
| Tetanus, diphteria | One dose every ten years | | | | | | |
| Measles, rubeola, mumps | ■ | ■ | One or two doses | | | | |
| Chickenpox | ■ | ■ | Two doses | | | ■ | |
| Influenza | One dose every year | | | | | | |
| Pneumococcus (polyvalent) | | One or two doses | | | | | |
| Hepatitis A | Two doses | | | | | | |
| Hepatitis B | Three doses | | | | Three doses | | |
| Meningococcus | One dose | | | One dose | One dose | | |

■ Recommended when there are other risk factors (chronic disease, occupational, behavior).

■ Contra-indicated.

ted diseases). It's possible, in this way, to have agenda about age groups or about risk categories. The mission of our College works in the following directions:

1. education to vaccines and immunization policy;
2. immunizations belong to GPs' daily practice and their scientific knowledge;
3. to offer tools of education and information;
4. to invite pharmaceutical industries make information service to primary care doctors;
5. to provide GPs innovating tools to value own practice, understand the weakness and criticism and supply solving to improve immunizations in adults and in elderly people.

## A governance tool for immunizations

MilleGPG (Mille General Practice Governance) is an informatic tool able to have an active interaction with the most spread electronic patient data record (Millewin®) in Italy. This application has been developed in collaboration with Italian College of General Practitioners (SIMG). MilleGPG provides GPs with a series of "dashboards" by which they can check several performance indicators. More than 200 performance indicators (epidemiological, ongoing and outcome) are embedded MilleGPG encompassing three main domains (clinical audit, appropriateness and risk management [8]. All indicators have been conceived according to international clinical guidelines during several meetings involving GPs and specialists. These indicators allow the verification of the GP's activities. When GP wants to analyze the cohorts of patients with chronic disease (for example patients with chronic obstructive pulmonary disease or with diabetes or with heart failure) in the domain "Risk Management & Prevention", it's possible to have the list of patients under 65 years old that should receive influenza vaccine. This list can be clean from patients that already have received the vaccine. The other can be recall or in a proactive way (every time patient comes in office for a prescription, the nurse or the doctor receive an alert on the patient record) or call the patient by mail or e-mail. This model can be replicated for other immunizations and in this way each GP (or group) can act a real governance of immunizations.

## Conclusions

Currently, every medical performance can be measured and improved. GP should adopt a systematic approach to immunization programs that includes educating patients and office staff using reliable sources of information, standing protocols during patient encounters and all practice management resources. Recall and reminder systems have resulted in increases of up to 20 percent in rate of vaccination [9]. Synergic policies of education, information and professional tools can improve the competences and behaviours for benefit to patients and society.

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■ Correspondence: Aurelio Sessa, via Cavour 26, 21051 Arcisate (VA), Italy - Tel. +39 348 2619602 - E-mail: sessa.aurelio@simg.it

Review

# Lessons learnt over two decades of vaccination against hepatitis B in Italy

L. ROMANÒ, C. GALLI, C. TAGLIACARNE, A.R. ZANETTI
Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Italy

Key words

Hepatitis B • Vaccination • HBV mutants

Summary

*This article reviews topics covered and discussed at the Meeting: "Vaccini e vaccinazioni. Migliorare l'oggi e preparare il domani", held in Genoa, Italy, on 12 September 2014. Data presented at the meeting, clearly showed that: 1) hepatitis B vaccination can confer long-term protection and there is no need for booster in immunocompetent vaccinees; 2) vaccination is highly effective in protecting population from clinical acute or chronic HBV infections, including hepatocellular carcinoma; 3) children vaccinated as infants with hexavalent vaccines maintain immunological memory 5 years after priming, but further studies are needed to assess whether immunity persists during the adolescence and adulthood when risk of exposure to HBV becomes higher; 4) the emergence of vaccine-escape mutants and Pol-gene mutants during antiviral therapy – which can result in changes in the S-gene – is of some concern, but at present there is no evidence that such mutants may pose a threat to the established programs of vaccination.*

## Introduction

Viral hepatitis B is a serious health problem throughout the world, being a leading cause of acute and chronic liver disease including cirrhosis and primary liver cancer, which ranks as the 3rd cause of cancer deaths worldwide. Globally, over 350 million people are chronic carriers of hepatitis B virus (HBV), more than 500,000 die each year from HBV-related diseases, and approximately 4.5 million people are newly infected yearly. The good news is that hepatitis B is now considered a largely treatable and preventable disease thanks to the availability of effective antiviral drugs and the implementation of several public health measures, including vaccination. Effective vaccines have been available since the early '80s and have proved highly successful to control and prevent hepatitis B and its severe sequelae. Following WHO recommendations, at present 181 countries in the world have implemented programs of hepatitis B vaccination with success both in term of safety and effectiveness.
This article reviews topics covered and discussed at the "Vaccini e vaccinazioni. Migliorare l'oggi e preparare il domani" Meeting held in Genoa, Italy, on 12 September 2014.

## Is a booster dose of hepatitis B vaccine required to maintain long-term protection?

Hepatitis B vaccination has been administered to hundreds of milion people of all ages showing an excellent level of safety and effectiveness in protecting people from developing clinical acute or chronic HBV infection. Following a complete course of vaccination (3 doses given at 0, 1, and 6 months), seroprotection rates (anti-HBs antibody at level ≥ 10 mIU/ml) are reached in > 95% of healthy children and adolescents, and in > 90% of healthy adults. Evidence shows that hepatitis B vaccine-induced anti-HBs antibody concentration declines over time and that the kinetics of decay depends on the magnitude of the peak antibody level achieved after primary immunization. In other words, the higher is the titer after primary vaccination course, the longer the antibody persists. Loss of protective antibody over time does necessarily means loss of protection since the immunological memory for HBsAg (hepatitis B surface antigen) can outlast the presence of antibody. Indeed, memory B and T cells are likely to persist beyond detectable anti-HBs antibody. Vaccinees who lost antibody usually show a rapid and strong anamnestic response when boosted or exposed to HBV [1-5].
These data clearly indicate that a strong immunological memory persists more than 20 years after primary immunization providing protection against clinical disease and the development of the carrier state [6-8]. Thus, based on current scientific evidence there is no need to administer booster doses of vaccine to sustain long-term protection in the general population. Such conclusion is based on data collected during the past 15-20 years and applies to both low and hyper-endemic areas of the world.
However, a booster dose could be provided to non- responders and some "at risk groups" (e.g., health care workers and immunocompromised individuals).
Recently, an increased number of failures to develop a response following a booster dose (the so-called boost-

ability) has been reported in some Asiatic countries. Waining of the ability to respond a booster dose seems to be more frequent in individuals vaccinated at birth with poor responses to priming.
Surveillance and additional follow up are needed to clarify this issue.

## Do children immunized as infants with hexavalent vaccines maintain protection over time?

In 2000, two hexavalent vaccines (Hexavac and Infanrix Hexa) were licensed in Europe for vaccinating children against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive infections caused by *Haemophylus influenzae* b. In 2005, Hexavac was suspended as a precautionary measure due to concern about long-term protection against hepatitis B, while no actions were taken over Infanrix Hexa [9]. Until suspension, approximately 10 million doses of Hexavac had been distributed globally, especially in Germany, Austria, and Italy. A crucial question is whether infants vaccinated with Hexavac maintain protection over time or require a booster vaccination to sustain immunity.
A large randomized, multicenter study carried out in over 1500 Italian children primed as infants with hexavalent vaccines 5 years earlier showed that 83.2% of those vaccinated with Infanrix Hexa maintained antibody over the protective level (≥ 10 mIU/ml) compared to 38.4% of those who were treated with Hexavac. Also GMC was higher in the former than in the latter group (61.3 mIU/ml *vs* 4.5 mIU/ml; $p < 0.0001$). Following a booster with a single dose of monovalent vaccine, both groups of vaccinees (either treated with Infanrix Hexa or with Hexavac) had similar good anamnestic responses both in terms of percentages of responders and GMCs, regardless of which hexavalent vaccine they had been primed with [10]. These data were confirmed and extended by other studies [11, 12].
The conclusion from these data is that routine booster doses of vaccine do not seem necessary to sustain immunity in children primed with hexavalent vaccines, even though follow-up beyond 5 years is necessary to assess whether protection can last during adolescence and adulthood when risk behavior of exposure to HBV through sexual activity or intravenous drug-taking is expected to increase.
A follow up study carried out in adolescents primed as infants 10 years before is currently in progress in Italy, and results will be available in 2015.

## Are HBV-escape mutants a matter of concern?

Hepatitis B neutralizing (protective) antibodies (anti-HBs) induced by vaccination are targeted largely towards the amino acid hydrophilic region known as the common a determinant which is present on the outer protein coat or surface antigen (HBsAg), spanning amino acids 124-147. This provides protection against all HBV genotypes (from A to H) and is responsible for the broad immunity afforded by hepatitis B vaccination. Thus, alterations of residues within this region of the surface antigen may determine conformational changes that can allow replication of the mutated HBV in vaccinated people.
An important mutation in the surface antigen region was identified in Italy some 25 years ago in infants born to HBsAg carrier mothers who developed breakthrough infections despite having received HBIG and vaccine at birth [13-15]. This virus had a point mutation from guanosine to adenosine at nucleotide position 587, resulting in aa substitution from glycine (G) to arginine (R) at position 145 in the a determinant. Since the G145R substitution alters the projecting loop (aa 139-147) of the a determinant, the neutralizing antibodies induced by vaccination are no longer able to recognize the mutated epitope. Besides G145R, other S-gene mutations potentially able to evade neutralizing anti-HBs and infect vaccinated people have been described worldwide [16-19].
In addition, the emergence of polymerase mutants associated with resistance to treatment with nucleos(t)ide analogues can select viruses with crucial changes in the overlapping S-gene, potentially able to alter the S protein immunoreactivity [20-22]. Thus the increasing use of such drugs may cause the emergence of mutants potentially able to escape vaccine-induced immunity and to infect vaccinees.
Despite concern, at present the overall impact of such mutants seems to be low and they do not pose a public health threat or a need to modify the established hepatitis B vaccination programs.

## Is hepatitis B vaccination effective in preventing liver cancer?

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death in humans and hepatitis B virus (HBV) is the most common etiological cause of HCC in the world, particularly in Asia, the Middle East, Africa and southern parts of Eastern and Central Europe. Chronic HBV infection can lead to chronic hepatitis, cirrhosis and HCC; it is estimated that chronic carriers of HBV are 100 times more likely to develop HCC than uninfected people. Thus prevention of chronic hepatitis B – through vaccination – can successfully prevent the risk of developing HBV-related cancer. Taiwan, a country where the universal HBV vaccination of newborns was implemented in 1984, is perhaps the best example of an area with previously high endemicity showing a substantial decrease over time of the burden of hepatitis B and HBV-related diseases, including HCC [23-26]. A study carried out by Chien et al, showed striking differences in HCC incidence (0.293 *vs* 0.117 per 100,000 person-years) between vaccinated and unvaccinated newborns 20 years after the implementation of vaccination, providing evidence that hepatitis B vaccination can

significantly prevent the long-term risk of HCC [27]. In Alaska, McMahon et al showed that following vaccination, the incidence of HCC in people < 20 years dropped from 3 per 100,00 in 1984-1988 to zero in 1995-1999, and no cases have occurred since 1999 [28].
All this clearly shows that anti-hepatitis B vaccination is a successful way to control and prevent HCC, indicating the hepatitis B vaccine as the first vaccine against a major human cancer.

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■ Correspondence: Alessandro R. Zanetti, Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, via C. Pascal 36, 20133 Milano, Italy - Tel. +39 0250315126 - Fax +39 0250315120 - E-mail: alessandro.zanetti@unimi.it

REVIEW

# Epidemiology of cancers of infectious origin and prevention strategies

S. DE FLORA, S. LA MAESTRA
Department of Health Sciences, University of Genoa, Italy

Key words

Cancer • Infectious diseases • Prevention

Summary

*Infectious and parasitic diseases represent the third cause of cancer worldwide. A number of infectious and parasitic agents have been suspected or recognized to be associated with human cancers, including DNA viruses, such as papillomaviruses (several HPV types), herpesviruses (EBV and KSHV), polyomaviruses (SV40, MCV, BK, and JCV), and hepadnaviruses (HBV); RNA viruses, such as flaviviruses (HCV), defective viruses (HDV), and retroviruses (HTLV-I, HTLV-II, HIV-1, HIV-2,HERV-K, and XMRV); bacteria, such as H. pylori, S. typhi, S. bovis, Bartonella, and C. pneumoniae; protozoa, such as P. falciparum; trematodes, such as S. haematobium, S. japonicum, S. mansoni, O. viverrini, O. felineus, and C. sinensis. Each one of the chronic infections with H. pylori, HPV, and HBV/HCV is responsible for approximately the 5% of all human cancers. The primary prevention of infection-related cancers is addressed both to avoidance and eradication of chronic infections and to protection of the host organism. Vaccines provide fundamental tools for the prevention of infectious diseases and related cancers. The large-scale application of the HBV vaccine has already shown to favorably affect the epidemiological burden of primary hepatocellular carcinoma, and HPV vaccines have specifically been designed in order to prevent cervical cancer and other HPV-related cancers. The secondary prevention of infection-associated cancers has already found broad applications in the control of cervical cancer. Detection of early gastric cancer by endoscopy has been applied in Asian countries. Avoidance of local relapses, invasion, and metastasis may be achieved by applying tertiary prevention, which targets specific mechanisms, such as angiogenesis.*

## Epidemiology of infection-associated cancers

### Global burden

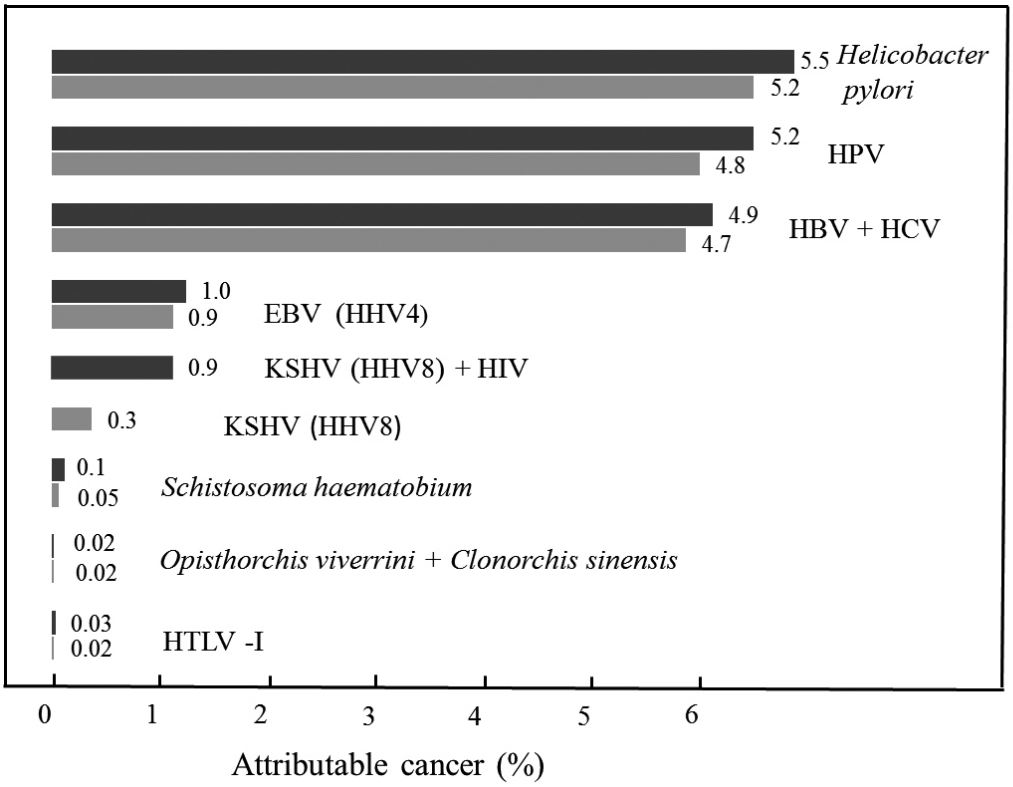
After dietary factors and tobacco smoke, infectious diseases represent the third leading cause of cancer worldwide. The population attributable fraction, which indicates the proportion of cancers associated with infectious and parasitic diseases, was estimated to be the 10% in the US population in 1981 [1], 10-20% in the UK population in 1998 [2], 3.6% in the French population in 2000 [3], 5% (range of acceptable estimates: 4-15%) in the UK population in 2005 [4], and 29.4% (31.7% in men and 25.3% in women) in the Chinese population in 2005 [5]. In the world population, it was estimated to be the 15.6% in 1990 [6], 17.8% in 2002 [7], and 16.1% in 2008 [8] . The last figure would correspond to about 2 million new cases of infection-related cancers diagnosed all over the world in 2008 [8].

The above estimates in the world population take into account the attributable fraction relative to the infections categorized in Group 1 by the International Agency for Research on Cancer (IARC), highlighting the infectious and parasitic agents for which there is sufficient evidence for carcinogenicity to humans [9]. Figure 1, which summarizes the results of two recent estimates [7, 8], shows, at a glance, the paramount importance of chronic infections in the etiology of cancer on a global scale. In particular, it appears that the chronic infections with *Helicobacter pylori*, human papillomaviruses (HPV), and hepatitis B (HBV) and C (HCV) viruses are each responsible for approximately the 5% of all human cancers and, altogether, they accounted for the 15.6% of human cancers worldwide in 2002 [7] and for the 14.7% in 2008 [8].

There are sharp differences in the epidemiological impact of infection-associated cancers between developing countries and developed countries, where the population attributable fraction has been estimated to be the 26.3% and 7.7% of cases, respectively [7] . These differences are due to geographical variations in the endemicity of infectious and parasitic agents associated with cancer as well as to the distinctive availability of preventive and therapeutic means towards both cancers and the related infectious diseases. Interestingly, lung cancer, colorectal cancers, breast cancer, and prostate cancer are, in terms of incidence, the 4 leading cancers in most geographical regions in the world [10]. The large majority of the exceptions to the above set of 4 cancers can be ascribed to cancers associated with infectious and parasitic diseases, which appear to contribute substantially to the disparities in cancer incidence between developed countries and developing countries.

A number of chronic viral, bacterial and protozoan infections and trematode infestations have been associated with human cancers affecting a variety of anatomical

**Fig. 1.** Fractions of cancers attributable to infectious agents categorized in IARC Group 1, as related to the total number of cancer cases in the world population in 2002 [7] (dark grey columns) and 2008 [8] (light grey columns).




sites. Table I reports a list of these agents, along with their categorization by IARC concerning the evidence of carcinogenicity to humans.

### Viral infections

Among DNA viruses, a dozen of HPV types, including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, have been allocated by IARC in Group 1, as their carcinogenicity to humans has been sufficiently demonstrated. Other HPV types are categorized either in Group 2A (probably carcinogenic), Group 2B (possibly carcinogenic) or Group 3 (inadequate evidence of carcinogenicity to humans). The overall fraction of cancer attributable to HPV infection was estimated to be the 5.2% in 2002 [7] and the 4.8% in 2008 [8]. The persistent infection of the uterine cervix by HPV is responsible for virtually the 100% of cervical cancers, although other factors may interact with HPV in the etiology of cervical cancer, which is the third leading cancer in the world female population in terms of mortality. In addition, HPV can target other sites in the anogenital region of women and/or men (vulva, vagina, penis, and anus), in the upper aerodigestive tract (mouth and oropharynx), and in the skin.

*Herpesviridae* include two important cancer-associated viruses, both of which are categorized in IARC Group 1. Each of them has been associated with almost the 1% of all human cancers (Fig. 1). One is the Epstein-Barr virus (EBV), or human herpersvirus 4 (HHV4), which causes infectious mononucleosis during adolescence and young adulthood while it is associated, in certain geographical areas, with several types of lymphoma. The most important EBV-related cancer is Burkitt's lymphoma, which is a quite common childhood cancer in sub-Saharan Africa. The most likely interpretation for the distinctive pathogenic spectrum of EBV in different geographical areas is a possible association with malaria where the Burkitt's lymphoma is prevalent (see below). In addition to lymphomas, EBV is associated with nasopharyngeal carcinoma, presumably in connection with genetic factors. The other cancer-associated virus of this family is the Kaposi's sarcoma-associated herpesvirus (KHSV), or human herpesvirus 8 (HHV8), which has been discovered in patients affected by acquired immunodeficiency syndrome (AIDS).

Four viruses belonging to the family of *polyomaviridae*, including SV40, MCV, BK, and JCV, have been evaluated for their association with human cancers [11]. SV40 (simian virus 40) has been suspected to be associated with mesothelioma. While its carcinogenicity to humans appears to be inadequate, there is sufficient evidence for SV40 carcinogenicity in experimental animals, also in association with asbestos. Nevertheless, SV40 has been allocated by IARC in Group 3, indicating that this virus is not classifiable as to its carcinogenicity to humans. MCV (Merkel cell virus) has been associated with MCC (Merkel cell carcinoma). Being its carcinogenicity not supported by studies in experimental animals, it has been

**Tab. I.** Pathogenic agents suspected or recognized to be associated with human cancers, and their allocation in IARC Groups according to the evidence of carcinogenicity to humans.

| Pathogenic agent[1] | IARC Group[2] |
|---|---|
| | |
| **DNA viruses** | |
| HPV, alpha types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 | 1 |
| HPV, alpha type 68 | 2A |
| HPV, alpha types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85 and 97,and beta types 5 and 8 | 2B |
| HPV, alpha types 6 and 11, other beta and gamma types | 3 |
| EBV (HHV4) | 1 |
| KSHV (HHV8) | 1 |
| SV40 | 3 |
| MCV | 2A |
| BKV | 2B |
| JCV | 2B |
| HBV | 1 |
| | |
| **RNA viruses** | |
| HCV | 1 |
| HDV | 3 |
| HTLV-I | 1 |
| HTLV-II | 3 |
| HIV-1 | 1 |
| HIV-2 | 2B |
| HERV-K | NA |
| XMRV | NA |
| | |
| **Bacteria** | |
| *Helicobacter pylori* | 1 |
| *Salmonella typhi* | NA |
| *Streptococcus bovis* | NA |
| Bartonella species | NA |
| *Chlamidophila pneumoniae* | NA |
| | |
| **Protozoa** | |
| *Plasmodium falciparum* | 2A |
| | |
| **Trematodes** | |
| *Schistosoma haematobium* | 1 |
| *Schistosoma japonicum* | 2B |
| *Schistosoma mansoni* | 3 |
| *Opistorchis viverrini* | 1 |
| *Opistorchis felineus* | 3 |
| *Chlonorchis sinensis* | 1 |

[1] See text for acronyms.

[2] Group 1, sufficient evidence of carcinogenicity to humans; Group 2A, probably carcinogenic; Group 2 B, possibly carcinogenic; Group 3, inadequate evidence of carcinogenicity to humans; NA, not available.

categorized as probably carcinogenic to humans (Group 2A). Two other polyomaviruses, BKV and JCV, were classified as possibly carcinogenic to humans (Group 2B) because the evidence for carcinogenicity to animals is sufficient, whereas their carcinogenicity to humans was evaluated to be inadequate. Both BK and JC are the initials of the patients from whom the viruses were isolated for the first time. In particular, BKV was found to induce a broad variety of tumors, also depending on the administration route, in hamsters, rats, and mice, but human data for prostate cancer and other types of cancer are inconsistent. Likewise, brain tumors were induced in monkeys and hamsters injected intracerebrally with JVC, but there is no clear association between JCV infection in humans and cancers [11].

HBV and HCV are hepatotropic viruses whose infection may evolve into chronic viral hepatitis. They are quite different viruses, being HBV a DNA virus belonging to the family of *hepadnaviridae*, whereas HCV is an RNA virus belonging to the family of *flaviviridae*. Both viruses are allocated in IARC Group 1 and, collectively, they were estimated to be responsible for the 4.9% of cancers in the world population in 2002 [7] and for the 4.7% in 2008 [8]. They have been associated with the 85.5% of cases of hepatocellular carcinomas (HCC), the 54.4% of which is attributable to HBV and the 31.1% is attributable to HCV [7]. The HBV nucleocapsid encloses the circular viral DNA, which is not fully double-stranded, and a DNA polymerase that has reverse transcriptase activity. A variety of mechanisms, spanning from integration of HBV DNA into the cellular genome to induction of cellular oncogenes by HBV gene products (e.g., HBx-Ag), deletion or mutation of tumor suppressor genes, and liver cirrhosis with inflammation, necrosis and regeneration , have been proposed as mechanisms involved in HBV carcinogenesis. Our studies have highlighted the importance of synergisms with chemical hepatocarcinogens (e.g., aflatoxin B1 and food pyrolysis products), whose metabolic activation is enhanced in the liver both of humans infected with HBV and of woodchucks infected with WHV (woodchuck hepatitis virus), which shares similarities with HBV [12-15]. The hepatitis D virus (HDV), or hepatitis delta antigen, having a circular RNA genome and needing the surface antigen of HBV (HBsAg) to establish infection in humans either as a co-infection or a superinfection, was classified in Group 3 by IARC several years ago [16], as the demonstration of HDV contribution to HCC induction by HBV was not adequate. However, more recently it has been suggested that the risk of hepatocellular carcinoma is higher when HBV is superinfected with HDV [17].

The RNA strands of *retroviruses* are complexed with reverse transcriptase and are thus transcribed into a double-stranded DNA that is inserted into the host genome, an obligatory step for their replication [18]. HTLV-I (human T-cell lymphotropic virus type 1) has been associated with adult T cell leukemia/lymphoma and it is allocated in IARC Group 1, whereas HTLV-II is in Group 3. HIV-1 (human immunodeficiency virus type 1) is the etiological agent of AIDS (acquired immune deficiency syndrome), which, due to immunodeficiency, has been associated with several human cancers and especially with KHSV-related Kaposi's sarcoma and non-Hodgkin's lymphoma. HIV-2 is possibly carcinogenic to humans. Two other retroviruses have been suspected to be associated with human cancers. One is HERV-K (hu-

man endogenous retrovirus), which may be involved in breast carcinogenesis [19], and the other one is XMRV (xenotropic murine leukemia-related virus), a chimeric, laboratory-derived gammaretrovirus that, interestingly, arose from the recombination of two endogenous mouse viruses. XMRV was suspected to be associated with prostate cancer [20].

### Bacterial infections

The prototype of cancer-associated bacteria is *H. pylori*, which is categorized in IARC Group 1 and was responsible for the 5.5% of cancers in the world in 2002 [7] and for the 5.2% in 2008 [8]. It has been estimated to account for the 63.4% [7] or 80.0% [19] of gastric cancers, specifically non-cardia gastric cancer. In addition, the chronic infection of the stomach with this bacterium is associated with MALT (mucosa-associated lymphoid tissue lymphoma). The intriguing issue is that about two-thirds of the world population, with some geographic variations, are carriers of *H. pylori*, and luckily only a small fraction of colonized individuals develop gastric cancer. We demonstrated that both bacterial and host gene polymorphisms affect oxidative stress and DNA damage, which is believed to represent a key mechanism in the pathogenesis of gastric cancer [21].
Among other bacteria, *Salmonella typhi* and *Streptococcus bovis* have been suspected of being associated with gallbladder carcinoma and colorectal cancer, respectively [22]. The persistent infection of erythrocytes and endothelial cells with Bartonella can trigger angiogenesis and lead to vascular tumor formation in humans, and *Chlamydophila pneumoniae* has been suspected of being associated with lung cancer [23].

### Protozoan infections

*Plasmodium falciparum* infection in holoendemic areas is probably carcinogenic to humans (IARC Group 2A) because, in the absence of any adequate evidence in experimental animals, there is limited evidence for an association between malaria caused by infection with that protozoan species and cancer. In particular, it is well demonstrated that *P. falciparum* reactivates EBV thereby contributing to Burkitt's lymphoma etiology [11].

### Trematode infestations

Some of the flatworms belonging to the Schistosoma genus, also known as blood flukes, have been investigated for their association with human cancers, especially in certain geographical areas. There is sufficient evidence for the ability of *S. haematobium* to cause urinary bladder cancer, whereas *S. japonicum* is possibly associated with colorectal and liver cancers, and there is inadequate evidence for the carcinogenicity of *S. mansoni.* Among the flatworms known as river flukes, there is sufficient evidence for the role of *Opistorchis viverrini* in inducing cholangiocarcinoma, while the evidence for *Opistorchis felineus* is evaluated to be inadequate. The same cancer is associated with infestation of the human common bile duct and gallbladder with the Chinese liver fluke (*Clonorchis sinensis*) [9].

## Prevention strategies for infection-associated cancers

### Primary prevention

The primary prevention of infection-related cancers is addressed both to avoid and eradicate chronic infections and infestations and to defend the host organism at a time when a subject is still apparently healthy. Therefore, the first line of defence is to prevent the infectious and parasitic disease, a goal that can be pursued by means of both aspecific and specific measures.
Vaccines play a fundamental role among the specific tools available to prevent some cancer-related infections. While the development of candidate vaccines against certain agents, such as HCV, HIV, *H. pylori*, and *P. falciparum*, is still in progress and suffers from technical problems, other vaccines are extensively used worldwide and hold great promises in cancer prevention. One of them is the hepatitis B vaccine, which has been introduced into routine infant immunization programs since 1992. The impact of anti-HBV vaccination on HCC epidemiology has already been demonstrated in Taiwan, where the universal HBV vaccination program, launched in 1984, reduced the prevalence of HBV to approximately one-tenth. In parallel, evidence was provided that HCC incidence was decreased as a consequence of the vaccination in children aged 6-14 years and, later on, also in early adulthood [24]. Failures to prevent HCC depended mostly on the unsuccessful control of HBV infection of maternal origin. Besides early vaccination of infants, administration of hepatitis B immunoglobulin immediately after birth, and even antiviral agent during the third trimester of pregnancy are possible strategies to block mother-to-infant transmission of HBV and to prevent HCC [25].
The HBV vaccine is the first example of cancer-preventive vaccine in humans, proving evidence that prevention of an infectious disease can prevent the related cancer. On the other hand, HPV vaccines are the first example of vaccines that have specifically been designed to prevent HPV-related cancers in humans. In fact, these vaccines, containing the HPV envelope protein L1 obtained by recombinant DNA techniques [23], target the HPV types responsible for the majority of cervical cancers and of non-cervical cancers as well. It can been foreseen that, together with secondary prevention, HPV vaccines will be successful in further reducing the burden of CIN (cervical intraepithelial neoplasia) and of HPV-related cancers.
Since infections need to become persistent in order to trigger the development of cancers, whichever is their mechanism of action, a further primary prevention strategy is to avoid chronicization of the disease. Thus, it is intriguing that the therapy of an infectious and parasitic disease becomes a tool to prevent the associated cancer. Besides a broad variety of drugs available to cure specific infectious diseases, examples of this kind of prevention include the HAART (high active antiretroviral therapy) for HIV infections, the new drugs avail-

able for the treatment of chronic hepatitis B and C, and the treatments to eradicate *H. pylori* infection in healthy asymptomatic subjects. For instance, in the Shandong Intervention Trial, two weeks of antibiotic treatment for *H. pylori* reduced the incidence of both precancerous gastric lesions and gastric cancer [26].

Furthermore, it should be taken into account that cancers are multifactorial in origin and that, besides infectious agents, other factors may contribute to the risk of developing the same cancers. Such a circumstance involves the implementation of integrated strategies for the primary prevention of these cancers. An extreme example is provided by HPV infections. Although HPV infections cause almost the 100% of cervical cancer cases, HPV can interact with other co-factors, such as tobacco smoking, hormonal contraceptive use, intake of nutrients, and co-infections with HSV (Herpes Simplex Virus) or *Chlamydia trachomatis* [27]. Other examples of interactions are either between different infectious agents, e.g., between HIV and KSHV in the pathogenesis of Kaposi's sarcoma or between EBV and *P. falciparum* in the pathogenesis of Burkitt's lymphoma, or between infectious agents and chemical carcinogens. For instance, the synergism between HBV and chemical hepatocarcinogens requires integrated strategies addressed to prevent chronic hepatitis B, to avoid exposures to chemical carcinogens, and to reinforce the body defence mechanisms by means of dietary and pharmacological agents.

#### SECONDARY PREVENTION

In case primary prevention fails avoiding the occurrence of a neoplastic lesion and the carcinogenic process starts its course, it is still possible to apply secondary prevention. Its goal is to detect a preneoplastic or a neoplastic lesion at an early stage and to intervene timely in order to stop progression of cancer.

An infection-associated cancer, the HPV-related cervical cancer, provides the most classical example of secondary prevention. The cytological analysis of epithelial cell smears, introduced by George Papanicolau more than 80 years ago, meets all the criteria requested for an oncological screening, from the epidemiological relevance of the disease to the poor invasivity of cell collection, fair performance of the test, low cost, and availability of a therapy to cure the disease. The large-scale application of the Pap test has remarkably reduced the burden of cervical cancer in all developed countries and has driven a wedge between different geographical areas. More recently, the HPV DNA testing, which analyzes the DNA of high risk HPV (HR HPV) in cervical cells, has been introduced and proposed to replace the Pap test as a first-screen method. This molecular approach detects an ongoing infection with HR HPV, which just testifies the risk of developing cervical cancer rather than an HPV-related cytological alteration. Thus, it is more sensitive but less specific and it needs confirmation by means of a cytological test and, if necessary, of colposcopy and biopsy.

Another example of secondary prevention applied to an infection-associated cancer is early gastric cancer, in which the disease is limited to mucosa and submucosa, so that removal of the lesion confers a survival rate after 5 years of 90%. Regression of premalignant lesions has been demonstrated after *H. pylori* eradication. Asian countries have implemented national screening programs for the detection of early gastric cancer, but in Western countries mass screening is not cost-effective and strategy has been directed to screen symptomatic individuals who are at higher risk of gastric cancer [28]. Serology testing for biomarkers such as pepsinogen, anti-*H. pylori* antibody and gastrin have been studied as an alternative to endoscopy [28].

#### TERTIARY PREVENTION

In the framework of the oncological patient management, tertiary prevention is addressed to cancer patients after therapy and it has the goal toprevent local relapses, invasion, and metastasis [29]. It can be pursued either by treating the cancer-related infection, e.g., by using antiviral agents to prevent recurrences in HBV-positive patients who have been cured for HCC [25], and/or by treating the neoplastic lesion. Besides traditional cytostatic drugs, the pharmacological armamentarium available for cancer therapy and tertiary prevention has been strengthened by introducing a variety of "smart drugs" that, rather than aspecifically kill cancer cells, try to target specific molecular mechanisms involved in cancer development and growth. A promising approach is to inhibit angiogenesis, which is a crucial mechanism in several infection-related cancers, by targeting VEGF (vascular endothelial growth factor) and other pro-angiogenetic factors [30]. Examples are HCC, having a hypervascular nature [31], bartonella-induced vascular tumors, and HIV/ KSHV-related Kaposi's sarcoma, which is a highly vascularized cancer. We demonstrated that the oral administration of the antioxidant agent NAC (*N*-acetylcysteine) reduced tumor growth in nude mice xenotransplanted with human KS cells and, in some cases, there was a complete regression of the neoplastic mass [32].

## Conclusions

The prevention of infection-associated cancers would be expected to control an important fraction of human cancers. Compared with cancers having a non-infectious nature, in principle these cancers would appear to be more easily avoidable because, besides the other strategies applicable to cancer prevention, it is sufficient to protect the body from exogenous pathogenic agents and to hamper the persistence of infections. Indeed, both primary prevention and secondary prevention measures have already proven to be successful in fighting certain cancers associated with infectious and parasitic diseases, which is highlighted by the sharp disparities between developed and developing countries in the incidence of these cancers. Future objectives in the prevention of infection-associated cancers include the improvement of our scientific knowledge about the mechanisms in-

volved, the development of new tools for the control of both infectious diseases and associated cancers, and the application of preventive measures on a global scale in order to fill the gap existing among different regions in the world.

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■ Correspondence: S. De Flora, Department of Health Sciences, University of Genoa, via A. Pastore 1, 16132 Italy - E-mail: sdf@unige.it

REVIEW

# Cancer prevention: state of the art and future prospects

I. VALLE[1], D. TRAMALLONI[2], N.L. BRAGAZZI[2]
[1] SSD "Popolazione a rischio", Health Prevention Department, Local Health Unit ASL 3 Genova, Italy;
[2] School of Public Health, Department of Health Sciences (DISSAL), Genova, Italy

Key words

Cancer prevention • Organized screening program • Vaccine

Summary

*Cancer imposes a heavy societal burden worldwide, in terms of both epidemiology and costs. The introduction of more sophisticated imaging and diagnostic techniques and advanced drugs that specifically target tumor cells is leading to increasingly expensive treatments, which may be affordable only for few patients. Prevention, and particularly primary prevention, is an effective way of addressing the challenging issue of cancer, since between a third and a half of cancers could be prevented on the basis of our current knowledge of risk factors. Moreover, prevention is cost-effective, its effects are not limited to high-risk subjects but extend to the entire population, and it is not dependent on socioeconomic status. Regulatory measures can have a broad impact, even on future generations; by empowering and educating subjects, promoting healthy behaviours and teaching self-care, they can trigger a virtuous cycle. In recent decades, oncology has shifted from being merely reactive to being proactive; this shift has led to the development of so-called "P4 medicine", where the 4 Ps stand for "preventive", "predictive", "personalized" and "participatory". Prevention programs are an important part of the effort to control cancer, as they are able to reduce both the incidence of cancer and mortality. For instance, screening for colorectal, breast and cervical cancer is reducing the burden of these common tumors. Anti-cancer vaccines, both prophylactic and therapeutic, constitute another important preventive tool. Although progress has been made in these areas, much remains to be done. With regard to screening programs, coverage could be increased by introducing new, more acceptable, less invasive tests, stratifying screening through correlation with anamnestic, clinical, radiological and genomic data (so-called "population-based personalized cancer screening"), and exploiting new information and communication technologies, such as smartphone applications or personalized text messages (so-called "screening 2.0"). Advocacy and recommendations by physicians can also play a role, in that eligible subjects need to be able to discuss their doubts and their perceived psycho-social barriers. However, new screening initiatives should be implemented only after a careful health technology assessment has been performed within the framework of evidence-based medicine, organized screening programs have been strengthened and opportunistic or spontaneous programs have been limited.*

## The global burden of cancer

Cancer imposes a heavy societal burden worldwide, in terms of both epidemiology and costs [1, 2]. Despite striking advances in the field of molecular oncology, combating cancer remains a challenge. The introduction of more sophisticated imaging and diagnostic techniques and advanced drugs that specifically target tumor cells (so-called individualized drug therapy) is driving up the costs of treatment [2, 3]. As a consequence, the benefit of these achievements may be scarcely affordable and the costs could dramatically impact on healthcare systems [2, 3]. Despite its alleged advantages, the implementation of genomics in routine clinical practice remains far from cost-effective [3].

As Vineis and Wild maintain [1], prevention, and specifically primary prevention, is a particularly effective way to address the challenging issue of cancer.

Primary and secondary prevention offers several advantages:

1. As such programs are population-based, they could benefit people other than those directly targeted [1].
2. As cancer has a long latency period, its causes and risk factors could be eliminated or reduced in the long term, thus yielding a broader impact on Public Health. Interventions are not limited to surgical or pharmacological treatments, but include a variety of programs and measures aimed at correcting unhealthy lifestyles and favouring continuous transformation, for example through regulation against occupational or environmental exposure to certain substances. By empowering and educating people, promoting healthy behaviors and teaching self care, a virtuous cycle can be set in motion, meaning that these preventive efforts do not need to be renewed with every generation. This is important in periods of economic and financial hardship, when public resources are scarce [1]. Moreover, some regulatory measures could help to prevent various types of cancer and other pathologies; for example, cigarette smoking, besides being associated with lung cancer, could lead to an increased risk of developing breast cancer [4], prostate cancer [5], lymphoma [6] and other diseases [7]. In addition, avoiding exposure to

carcinogenic substances may contribute to preventing other non-communicable diseases (NCDs), such as cardiovascular, reproductive, endocrine and dysmetabolic pathologies [1]. In conclusion, a single public health measure would have multiple, enduring "cascade effects" which a single clinical intervention would not have.

3) Prevention is cost-effective and can impact positively on socio-economic inequalities [8-12]. Since up to half of cancers could be prevented on the basis of present knowledge of etiopathogenesis and risk factors [1], preventive medicine can act as a rapid and effective means of connecting research with clinical practice [13].

Primary and secondary prevention should therefore be regarded as a priority for global cancer control [1, 14].

## Oncology in the framework of P4 medicine

In recent decades, oncology has shifted from being merely reactive and has adopted a proactive model within the framework of so-called "P4 medicine" [15, 16], where the 4 Ps stand for predictive, preventive, personalized and participatory. Advances in the field of molecular biology, high-throughput technologies (HTTs) and "omics" sciences, as well as in imaging techniques and mathematical and computational modelling, have led to the discovery of biomarkers which can be used to predict the onset, course and prognosis of tumors; this enables diagnosis, treatment and prevention to be correlated within a highly integrated, coherent framework. Rather than being "one-size-fits-all", P4 medicine is individually tailored to the specific needs of the patient. Screening and prevention play a major role in an approach that is gradually shifting from disease to wellness.

It should be emphasized that this new effort requires a holistic view at all levels [17]; cancer is a complex adaptive system (CAS), the etiopathogenesis of which can be unravelled only by means of a systems approach (systems biology and "omics" sciences). Cancer management requires multi-level system-based management [18]. Organized screening is a highly standardized form of "systems screening"; as it is constantly monitored through quality check and process indicators and relies on evidence-based protocols and guidelines, it differs from opportunistic or spontaneous screening [19].

In the system of systems (SoSs) perspective, cancer screening programs can be integrated into health promotion plans, becoming "teachable moments", during which people can be sensitized to the importance of proper nutrition, physical activity and other healthy behaviors [20]. In this way, as already mentioned, a virtuous cycle with cascade effects can be set in motion.

The following sections present an overview of the currently available organized cancer screening tests, a discussion of their present state and future prospects, and a brief look at the topic of anti-cancer vaccines.

### Prevention of cervical cancer

Cervical cancer is the tenth most frequent cancer and the third most common cancer in terms of mortality, after breast and colorectal cancer [21-23], though this trend is decreasing.

Risk factors for developing cervical cancer include: tobacco and alcohol consumption, a history of genital warts, early age on first sexual intercourse or first pregnancy, multiparity, sexual promiscuity and unprotected sex, a history of sexually transmitted diseases (STDs), low socio-economic status and low educational level, Human Immunodeficiency Virus (HIV) infection and other conditions resulting in immunosuppression [21-23].

Screening modalities include [21-23]: 1) cervical cytology (Papanicolau or Pap smear), which may be conventional or liquid-based (LBC), and may be assisted by automated screening technologies (ASTs) [24]; 2) colposcopy, which involves direct visual inspection (DVI) performed by using 3-5% acetic acid (VIA), 3-5% acetic acid and magnification (VIAM), or Lugol's iodine (VILI); and 3) HPV-DNA testing [25]. Other modalities, such as cervicoscopy, cervicography, colpohysteroscopy/microcolpohysteroscopy, speculoscopy (a magnified chemiluminescent screening examination) and polar probes (such as spectrophotometry/microspectrophotometry, Raman scattering and fluorescence spectroscopy), are still experimental and can be used as second-line techniques for the further evaluation and assessment of abnormal results. A next-generation assay, which is quite promising, is HPV mRNA testing [26-28].

According to the 2010 European Guidelines for Quality Assurance of Cervical Cancer Screening [29], the American Cancer Society (ACS), the American College of Obstetricians and Gynaecologists (ACOG) and the Centers for Disease Control and Prevention-Advisory Committee on Immunization Practices (CDC-ACIP), the age at which screening should be started is in the range of 20-30 years, but preferably not before 25 years (in Italy, for example, the age is 25 years). Women aged 21-29 years should undergo a Pap smear every 3 years, regardless of their sexual activity. If the result of the test is abnormal (such as atypical cells of undetermined significance, or ASCUS), the woman should undergo HPV-DNA testing [29, 30]. Women over the age of 29 years can be screened every 5 years with a combination of HPV-DNA testing and Pap smear. The age at which screening should be discontinued is in the range of 60-65 years of age (in Italy, for example, it is 65 years), in the absence of abnormal results [29, 30].

Recently, four European randomized controlled trials (RCTs) (Swedescreen in Sweden, POBASCAM in the Netherlands, ARTISTIC in Great Britain and NTCC in Italy) have shown that HPV-based screening started at the age of 30 years, with screening intervals of up to 5 years, is still effective in protecting women against invasive carcinoma [31]. However, although this strategy appears to be the most cost-effective, it is applied in few countries [32].

Compliance with cervical cancer screening programs is still unsatisfactory and strongly age-dependent [33].

Variables which can predict adherence to screening include educational level, culture, psychosocial issues and marital status [33, 34].
High-quality cervical screening helps to reduce the incidence of cervical cancer and mortality. In Italy, the incidence of squamous cell and invasive cancers has significantly decreased from 11.6/100,000 to 8.7/100,000 since the introduction of cervical screening [35].

### Prevention of colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in men, after lung and prostate cancer, and the second most frequent cancer in women after breast cancer, with more than 1,360,000 cases per year (10% of the total cancer burden). Its incidence increases with age, and more men than women are affected [36]. CRC is a major cause of cancer-related death, ranking fourth after lung, liver and stomach cancer [37].
Risk factors for developing CRC are: obesity [38], consumption of red and highly processed meat [39], tobacco and alcohol use, a history of inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease, a family history of inherited CRC, and syndromes such as familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) [40]. Vegetable consumption and physical activity are protective factors [41].
CRC can be screened in several ways [42, 43], the most commonly used method being the stool test, known as fecal occult blood test (FOBT). Variants of this test are the guaiac-based FOBT (gFOBT), the fecal immunochemical test (FIT) and the stool DNA test (sDNA).
In the event of positivity, flexible sigmoidoscopy (FS) or total colonoscopy (TC) can be performed [37]. Computed tomography (CT) scans (CT colonography, or CTC) can be used in those patients in whom TC is contraindicated or if it has not been possible to perform a complete TC [37].
Other tests, which are still experimental, are double-contrast barium enema (DCBE), colon capsule endoscopy (CCE) and high-resolution colonoscopy (HRC) [37]. The Epi proColon® 2.0 test (Epigenomics AG) is a highly sensitive and specific new-generation test; this assesses aberrant methylated patterns of the septin 9 gene, which is usually hypermethylated in CRC [44].
CRC screening should be started at the age of 50 years; subjects who are particularly at risk for CRC should be screened earlier and more frequently. According to the guidelines, screening options for eligible subjects include: FOBT every year; DCBE every 5 years; FS every 5 to 10 years, usually combined with FOBT every 1-3 years; virtual colonoscopy (VC) every 5 years; colonoscopy every 10 years. In the event of positivity, colonoscopy should be performed [37].
Adherence to the program is still low: for example, a recently published systematic review has found that in 2000, in the USA, only 34% of the population complied with CRC screening following the recommendations and guidelines [45]. It has been observed that doctors, particularly family doctors, play a major role in increasing participation by discussing the benefits and usefulness of screening with their patients [46, 47].
High-quality CRC screening [48] has been seen to reduce the incidence of CRC by 33% and mortality due to CRC by 43% [36].

### Prevention of breast cancer

Despite advances in treatment and diagnosis, breast cancer is still a serious Public Health concern [49], with 1,384,155 expected new cases worldwide and an estimated 459,000 deaths [49]. Moreover, both incidence and related mortality have increased by 18% since 2008. According to the ACS, breast cancer affects one in every eight women in the US. It is estimated that the annual global burden of breast cancer will reach 3.2 million new cases by 2050 [49].
Risk factors for developing a breast cancer include: breast size [50], lack of physical activity, overweight and obesity [51-53], infertility and nulliparity, first full-term pregnancy at the age of 30 years or later, early age on menarche, tobacco and alcohol use, hormone replacement therapy (HRT) such as oestrogen and progestin, exposure to diethylstilbestrol (DES), inherited genetic anomalies (BRCA1, BRCA2) [49, 53, 54], and Cowden and Li-Fraumeni syndrome [53, 54]. Breastfeeding and vegetable consumption are protective factors.
Mammography is the gold standard in early breast cancer detection; screening results are communicated by means of the highly standardized "breast imaging reporting and database system" (BI-RADS).
In 2009-2010, the US Preventive Services Task Force (USPSTF) issued new updated recommendations for routine mammography screening, after examining and comparatively assessing five different screening modalities: namely, screen-film two-dimensional (2D) mammography, clinical breast examination (CBE), breast self-examination (BSE), three-dimensional (3D) digital mammography (such as the Digital Breast Tomosynthesis, or DBT, recently approved by the Food and Drug Administration, FDA), and magnetic resonance imaging (MRI) [55]. Other screening modalities, such as thermography, are still experimental, while tissue-sampling approaches (fine-needle aspiration, or FNA, nipple aspiration or ductal lavage) are usually used for diagnostic purposes only. The USPSTF recommended against routine mammographic screening in women aged 40-49 years, unless the patient's history suggested it and after careful assessment of the benefits and harm. Biennial mammographic screening was recommended for women aged 50-74 years; no evidence of additional benefits or harms emerged with regard to CBE, while BSE was advised against. The USPSTF called for further studies on the clinical usefulness of digital mammography and MRI.
By contrast, the American College of Radiology (ACR), the American Society of Clinical Oncology (ASCO) and the Society of Breast Imaging (SBI) calculated that mammography, if not performed in women aged 40-49 years, would miss 19-33% of cancers and would sacrifice 33 years of life per 1,000 women screened. These

agencies therefore recommended routine screening mammography commencing at the age of 40 years.
A mathematical model seems to support the opinion of the USPSTF [56], since including women in their 40s would increase the number of false-positive cases by 53%. One solution could be the use of ultrasonography [57], which would enable radiologists to detect additional 3-4 cancers per 1,000 high-risk women screened [48]. Moreover, MRI and ultrasound as supplemental screening techniques would be particularly useful for women with extremely dense breasts [48]. However, implementation of this policy should be carefully evaluated by means of a cost-effectiveness analysis, in order to develop the best strategy.
Despite these controversies, breast cancer screening has undoubtedly contributed to reducing cancer mortality by 30-50% [58]. In Italy, after the introduction of organized mammography screening, the IMPACT working group found a statistically significant, steady reduction in the incidence of late-stage breast cancer from the third year onward, with the incidence rate ratio (IRR) declining from 0.81 to 0.71 [59]. This decline was more evident in three regions: Liguria, Tuscany and Lombardy [60]. However, coverage remains low (69.1%) [61].

## Anti-cancer vaccines

There are two kinds of anti-cancer vaccines: preventive (or prophylactic) and therapeutic vaccines. The former include anti-HPV vaccines (Gardasil® and Cervarix®) for the prevention of cervical cancer [62, 63], and anti-HBV vaccines for the prevention of hepatocellular carcinoma [64]. The latter are whole cell-, protein- and peptide-, dendritic cell-, gene-, or idiotype immunoglobulin-based vaccines [65].
Generally speaking, anti-cancer vaccines stimulate cytotoxic T lymphocytes (CTL) against tumor-associated antigens (TAA) or tumor-specific antigens (TSAs). Therapeutic anti-cancer vaccines have greatly benefited from forward vaccinology [66, 67], which uses advanced mass spectrometry (MS) approaches, thus enabling the design of customized vaccines. Currently, Oncophage® and Provenge® represent the two most successful approved anti-cancer vaccines.
The autologous heat shock protein (HSP)-based vaccine Oncophage® (HSP-peptide complex 96, HSPPC-96) was released in May 2008 in Russia for the treatment of kidney cancer patients at intermediate risk of disease recurrence. Clinical trials conducted among metastatic kidney cancer patients had shown a statistically significant improvement [68]. The second-generation autologous HSP-based vaccine, Vitespen®, a purified gp96-peptide complex, has yielded promising results in a variety of cancers, including CRC, glioblastoma, lung cancer, melanoma and renal cell carcinoma [69].
In April 2010, the FDA approved Sipuleucel-T (Provenge®, Dendreon) for metastatic prostate cancer [70]. This vaccine, which elicits CTLs against prostatic acid phosphatase (PAP), is obtained by using leukapheresis, isolating APCs and processing them with PAP crosslinked to the granulocyte-macrophage colony-stimulating factor (GM-CSF).
Other approved cancer vaccines are Nivolumab (Opdivo®, formerly known as MDX-1106, recently approved for melanoma and squamous non-small cell lung cancer, currently under clinical trial for further malignancies, including CRC and brain cancer), Ipilimumab (Yervoy®, approved for melanoma, under trial for bladder and prostate cancer) and Gendicine® (approved by the Chinese State Food and Drug Administration or CSFDA for the head and neck squamous cell carcinoma).
Cancer vaccines currently under clinical trial include Tremelimumab (also known as Ticilimumab or CP-675,206, under trial for mesothelioma, bladder cancer), DCvax® (for astrocytoma), BiovaxID™ (Dasiprotimut-T, under trial for follicular lymphoma), ProstVac-VF®/Tricom™ (under trial for prostate cancer), PanVac-VF™ (a poxviral-based cancer vaccine containing transgenes for the epithelial mucin 1 and carcinoembryonic antigen or CEA, currently under clinical trial for a variety of cancers, including breast and pancreatic tumor), MVax® (under trial for melanoma), OncoVax® (under trial for CRC), Reniale® (under trial for renal cancer) and a glycoprotein-100 (gp100)-based vaccine against melanoma [65, 68], among others.

## Future screening programs

In many countries, screening tests are also performed for lung cancer, melanoma, prostatic, oral, pancreatic and ovarian cancers. However, their unstructured application has resulted in poor or insufficient scientific evidence [71]. For example, clinical trials such as the European Randomized Study of Screening for Prostate (ERSSP) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [72] yielded conflicting results regarding the utility of Prostate Specific Antigen (PSA)-based screening for prostate cancer, since PSA has not proved superior to digital rectal examination (DRE) [71, 73]. We cannot, however, exclude the possibility that the introduction of more reliable biomarkers, such as MD-miniRNA, which could more effectively distinguish between prostatic hyperplasia and prostate cancer [74], will improve the efficacy of prostate cancer screening.
Further research and high-quality clinical trials are needed. The introduction of new screening programs should be considered only after a careful Health Technology Assessment (HTA) has been performed, and in the light of solid clinical recommendations in conformity with Evidence-Based Medicine (EBM) [75, 76].

## Future prospects and conclusions

In conclusion, prevention programs are an important weapon in the fight against cancer, and currently available evidence shows that they can contribute to reducing both the incidence of cancer and mortality. However, adherence to screening programs remains an issue to be addressed, in that screening tests are still underused [77]. A promising solution could be to personalize screening.

Stratification for population-based risk-adjusted screening programs could be performed by using *ad hoc* risk models. Since cancer is indeed a common complex disease, screening programs could benefit from the use of genomic information, whilst this is generally not so helpful to diagnosis and prediction at the individual level [78]. It is anticipated that merging personal anamnestic data with those from clinical and radiological examinations will give rise to a new discipline, termed radiogenomics, which would optimize personalized medicine by correlating imaging with genetic information [79].

Another scientific hint of the utility of "population-based personalized screening" is the intrinsic biological and genetic difference between screening-detected cancers and interval cancers (that is to say, cancers arising during inter-screening intervals) [79]. Genomics-based stratification could indicate the optimal screening interval. For example, in the field of breast cancer screening, applying genomics and targeting subjects in the top 25% of the risk distribution would include approximately half of all future breast cancer cases [80]. Moreover, one mathematical model showed that a breast cancer screening program based on age and polygenic risk, and which targeted women aged 35-79 years, would reduce the number of false positives, and therefore of unnecessary biopsies and surgical procedures [81, 82].

In order to increase coverage, physicians should strongly recommend screening programs and discuss their patients' doubts and perceived psycho-social barriers [83, 84]. Advocacy could play a major role, and Public Health professionals should discourage opportunistic screening. On the other hand, researchers should develop and investigate new, more acceptable, less invasive tests [37].

New information and communication technologies (ICTs), such as smart-phone applications (known as *apps*), personalized short message services (SMS) and texting [85], could also help to promote adherence to programs. "Screening 2.0" is a great opportunity, which is still underused [86].

In sum, oncology has seen great changes in recent decades; together with improvements in diagnosis and treatment, prevention has played a major role in reducing both the incidence of tumors and mortality. Advances in technology and social media and the discovery of new biomarkers are expected to bring additional benefits.

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## Abbreviations

2D: two-dimensional; 3D: three-dimensional; ACIP: Advisory Committee on Immunization Practices; ACOG: American College of Obstetricians and Gynaecologists; ACR: American College of Radiology; ACS: American Cancer Society; APCs: Antigen Preventing Cells; apps: applications for smart-phones and mobile devices; ASCO: American Society of Clinical Oncology; ASCUS: atypical cells of undetermined significance; ASTs: Automated Screening Technologies; BRCA1: Breast Cancer Type 1 susceptibility protein; BRCA2: Breast Cancer Type 2 susceptibility protein; BSE: Breast Self-Examination; CAS: Complex Adaptive System; CBE: clinical breast examination; CCE: colon capsule endoscopy; CDC: Centers for Disease Control and Prevention; CEA: carcinoembryonic antigen; CRC: Colorectal Cancer; CSFDA: Chinese State Food and Drug Administration; CT: computed tomography; CTC: CT colonography; CTLs: Cytotoxic T Lymphocytes; DBT: Digital Breast Tomosynthesis; DCBE: Double-Contrast Barium Enema; DES: Diethylstilbestrol; DNA: deoxyribonucleic acid; DRE: digital rectal examination; DVI: direct visual inspection; EBM: Evidence-Based Medicine; ERSSP: European Randomized Study of Screening for Prostate; FAP: familial adenomatous polyposis; FDA: Food and Drug Administration; FIT: fecal immunochemical test; FNA: fine-needle aspiration; FOBT: fecal occult blood test; FS: flexible sigmoidoscopy; gFOBT: guaiac-based FOBT; GM-CSF: granulocyte-macrophage colony-stimulating factor; HBV: Hepatitis B Virus; HC2: Hybrid Capture 2; HCV; Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HNPCC: hereditary nonpolyposis colorectal cancer; HPV: Human Papillomavirus; HRC: High-Resolution Colonoscopy; HRT: Hormone Replacement Therapy; HSP: Heat-Shock Protein; HSPPC-96: HSP-peptide complex 96; HTA: Health Technology Assessment; HTTs: High-Throughput Technologies; IBD: inflammatory bowel disease; ICTs: Information and Communication Technologies; IRR: incidence rate ratio; LBC: Liquid-Based Cytology; LMICs: Low and Middle Income Countries; mRNA: messenger RNA; NCDs: non-communicable diseases; P4 Medicine: predictive, preventive, personalized and participatory medicine; PAP: prostatic acid phosphatase; Pap smear: Papanicolau smear; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA: Prostatic Specific Antigen; RCT: Randomized Controlled Trial; SBI: Society of Breast Imaging; sDNA: stool DNA; SMS: Short Message Service; SoSs: System of Systems; STD: Sexually Transmitted Disease; US: United States of America; USPSTF: US Preventive Services Task Force; TC: total colonoscopy; TAAs: Tumor-Associated Antigens; TSA: Tumor-Specific Antigens; VC: Virtual Colonoscopy; VIA: visual inspection using 3%-5% acetic acid; VIAM: visual inspection using 3%-5% acetic acid and magnification; VILI: visual inspection using Lugol's iodine.

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■ Correspondence: Ivana Valle, SSD "Popolazione a rischio", Health Prevention Department, Local Health Unit ASL 3, via B. Agnese 1/c, 16151 Genova, Italy - Tel. +39 010 8498982 - Fax: +39 010 8499055 - E-mail: ivana.valle@asl3.liguria.it

Review

# Insights on common vaccinations in HIV-infection: efficacy and safety

L.A. NICOLINI, D.R. GIACOBBE, A. DI BIAGIO, C. VISCOLI
University of Genoa (DISSAL); Infectious Diseases Unit – IRCCS AOU San Martino-IST, Genoa, Italy

Key words

Vaccination • HIV • Efficacy

Summary

*HIV-infected patients are at increased risk for both vaccine-preventable diseases and their complications, with mortality rates higher than in non-HIV-infected individuals. Consequently, international guidelines generally recommend inactivated vaccines in HIV-patients, even if HIV-related immunodeficiency may impair efficacy; live vaccines are usually not recommended in these patients because of safety concerns. The aim of this short article is to review current knowledge about both efficacy and safety of vaccines in HIV-infected individuals.*

## Introduction

Human Immunodeficiency Virus (HIV) infection is a leading cause of morbidity and mortality [1]. If untreated, HIV leads to a progressive impairment of the cellular immunity, thus increasing the risk of opportunistic infections and malignancies [2, 3].
Parameters most commonly used to monitor the advancement of the disease include the plasmatic HIV viral load (HIV-RNA) and the serum CD4-T cell count [4]. Indeed, a detectable plasmatic HIV-RNA reflects an active viral replication, while a reduced CD4-T cell count suggests an impoverishment of the immune response against infections and cancers. On the other hand, an undetectable plasmatic HIV-RNA and an increased serum CD4-T cell count are both markers of favorable response to antiretroviral therapy (ART), the latter being also associated with a dramatic reduction in the risk of opportunistic infections [5, 6]. However, despite immunovirological control with ART, HIV infection remains associated with residual perturbations of the immune cellular response, including both T- and B-cells [7]. If we accept the idea that even in immunovirological controlled HIV-infected patients the immune system does not work normally, it is conceivable that immune response to vaccines may remain sub-optimal, as well.
Attempting to deal with this important matter, in this paper we review current literature about efficacy of vaccinations in HIV-infected adults, as well as safety concerns regarding the administration of live vaccines.

## Impact of vaccine-preventable diseases in HIV patients

HIV-infected patients are at increased risk for the development of both vaccine-preventable diseases and their complications, with higher mortality rates than in non-HIV-infected individuals.
*Streptococcus pneumoniae* pneumonia is a leading cause of death worldwide, although its survival has dramatically improved in the last century due to improved nutrition and life conditions together with public health measures and the advent of the antibiotic era [8]. As regards the impact of HIV infection on the outcome of this disease, mortality of *S. pneumoniae* pneumonia and/or bacteremia has been reported to be higher in HIV-infected patients than in HIV non-infected subjects, even after the introduction of ART [9, 10].
An association between increased mortality and HIV infection has also been reported for influenza in patients with severe immunodeficiency, with high influenza-attributable risk of acute cardiopulmonary event [11]. For these reasons both anti-pneumococcal and anti-influenza vaccines are recommended for HIV-infected individuals, with preference, in the case of influenza, for inactivated vaccines [12-14]. An inactivated influenza vaccine should thus be administered annually to all HIV-infected individuals [12]. Of note, avoiding the development of influenza through vaccination is also an indirect way to prevent bacterial pneumonia which can occur as a complication of the viral disease [12].
The considerable impact of some other vaccine-preventable diseases in HIV-infected patients is not only related to their acute-phase mortality, but it also derives from the high prevalence of these diseases in the HIV population, with effects on long-term morbidity and mortality. For example, international guidelines recommend vaccination of HIV-infected patients against hepatitis A virus (HAV), hepatitis B virus (HBV) and human papillomavirus (HPV), even if complete and reliable data regarding efficacy of these vaccines in HIV-infected patients are not available [13].

It has been demonstrated that HIV-infected patients are at higher risk for HBV infection in comparison with non-HIV-infected subjects, since HBV shares the same routes of transmission of HIV. In addition, HBV infection significantly increases liver-related mortality in HIV-1-infected patient [15], especially for those with low CD4-T nadir count [15, 16]. Moreover, due to some shared risk factors (i.e., intravenous drug use and being a man who have sex with man), also vaccination against HAV should be considered in HIV-infected patients [17, 18].

Similarly to hepatotropic viruses, the prevalence of HPV-related diseases in HIV-infected patients is higher than in non-HIV-infected individuals. Therefore, HIV women are at higher risk for developing cervical intraepithelial neoplasm and cervical cancer in comparison with the general population [19-23]. Accordingly, HPV vaccine is strongly recommended for HIV-infected girls aged 9 through 26 years by Italian and ACIP guidelines, while only a moderate recommendation is provided by American guidelines, due to the lack of complete efficacy data in the HIV population [12-14].

Finally and obviously, HIV-infected individuals are at risk of preventable diseases such as tetanus, diphtheria and pertussis with no difference with respect to the general population, and should therefore receive specific vaccinations.

Detailed international schedules for different types of vaccinations in both HIV-infected and non-HIV-infected patients can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html [14].

## Efficacy and immunogenicity of different vaccines in the HIV setting

The vaccine efficacy in preventing disease in HIV-infected patients has been demonstrated for *S. pneumoniae* and influenza viruses associated diseases.

As regards *S. pneumoniae*, Rodriguez-Barradas et al compared 692 non-HIV-infected and 934 HIV-infected subjects in a randomized clinical trial, the 59% of whom were vaccinated with the 23-valent pneumococcal polysaccharide vaccine [24]. The primary endpoint was time to the first pneumonia event, after controlling for HIV-specific variables. They found that the anti-pneumococcal vaccination significantly reduced the risk of pneumonia (HR 0.65, 95% CI 0.42-1.00, p = 0.05) in HIV-infected patients, while the impact of vaccination in non-HIV-infected was not significant [24].

A recent systematic review investigated the efficacy and the effectiveness of influenza vaccination in 1562 HIV-patients [25]. Data was retrieved from 3 randomized-controlled trials (RCT) and 3 observational studies. The authors observed a pooled efficacy of 85% in preventing laboratory-confirmed influenza (95% CI 22-97%) among adult patients, while this effect was not confirmed in young children [25]. In the 3 observational studies, a favorable effect of vaccination was reported only in one of them, with an effectiveness of 71% (95% CI 44-85%) in preventing laboratory-confirmed influenza [15]. However, it should be noted that a high risk of bias was reported in all the 3 observational studies included [15].

For other vaccines, such as those against HBV, HAV, and HPV, immunogenicity has been used as a surrogate marker for clinical effectiveness in several observational studies, while no randomized trials have still validated their efficacy and effectiveness in preventing disease [26].

Two studies compared rates of serological response to HBV vaccination in HIV-infected vs. non-HIV-infected individuals. In the first, Irungu et al. found that the nonresponse to HBV vaccine was higher in 310 HIV-infected patients than in 293 non-HIV-infected subjects (35% *vs* 14%, $p < 0.001$) [27]. In the second study, Collier et al. compared 16 HIV-infected and 68 non-HIV-infected children and found that subjects who were HIV-infected frequently lacked protective levels of anti-HBs titers after three doses of 20 μg of recombinant HBsAg in comparison to HIV-uninfected individuals (44% *vs* 9%, $p = 0.002$) [28].

About HAV, Neilsen et al. investigated 90 HIV-infected and 44 non-HIV-infected subjects, both receiving a 2 dose vaccination course [29]. The authors observed that among patients tested for seroconversion after two vaccination doses the HAV seroconversion rate was significantly lower in HIV-positive patients in comparison with HIV-negative subjects (88.2%% *vs* 100%, respectively, $p = 0.03$) [29]. In addition, in the subgroup of HIV-infected patients, baseline CD4-T cell count was considerably higher in those who showed serological response to HAV vaccination than in those who did not (mean baseline CD4-T cell count 540/μL *vs* 280/μL, respectively, $p = 0.033$) [29]. On the other hand, Wallace and coworkers studied HAV seroconversion rates after vaccination among 90 HIV-infected and 90 non-HIV-infected patients. In this exerience, antibody responses were sustained among the non-HIV-infected subjects (100%, 95%CI 95-100) and HIV-infected subjects with CD4-T cell count higher than 300/μL (100%, 95%CI 87-100), but they decreased among patients who had had CD4-T cell counts lower than 300 cells/mm$^3$ at enrollment (87%, 95%CI, 66-97) [30]. Finally, Tseng et al. reported an unfavorable association between HIV infection and response to HAV vaccination independently from receiving either two or three doses of HAV vaccine ($p = 0.01$) [31].

With regard to HPV vaccination in adults, a phase 2 open-label multicenter trial found the 3-dose quadrivalent HPV vaccine to be immunogenic in 99 young HIV-infected women aged 16-23 years. The observed seroconversion rates were as high as 100% for HPV-6, 11, 16, and 18 among women on ART [32]. Moreover, Wilkin et al. found that the same vaccine was immunogenic among 109 HIV-infected men ≥ 18 years, with seroconversion rates of 98% for HPV-6 (59/60), 99% for HPV- 11 (67/68), 100% for HPV-16 (62/62), and 95% (74/78) for HPV-18 (74/78) [33].

Finally, optimal revaccination strategies for patients with no serological response to vaccination schedules are still under debate.

## Impact of vaccination on HIV-infection

Interestingly, some authors have highlighted responses to vaccination from an HIV standpoint, aiming at elucidating any possible impact of different vaccines on the course of the HIV-related disease.
For influenza vaccination, Durando et al. did not report any increase in both HIV replication and CD4-T cell count following influenza vaccination with two different virus subunit vaccines at three time points, whereas Calmy et al. detected transient increases in HIV-RNA levels in 3 of 66 (4.5%) previously aviremic HIV patients who received two doses of an AS03-adjuvated flu pandemic vaccine [34]. Of note, these transient increases did not recur after boosting with a non-AS03-adjuvated influenza vaccine. Similarly, Onlamoon et al. observed detectable plasmatic HIV-RNA levels among 8/37 previously aviremic HIV-infected patients (22%) who received a monovalent non-adjuvated influenza A H1N1 2009 vaccine, even though a concomitant increase in lymphocytes activation was not observed [35].
Two clinical trials did not report any effect on plasmatic HIV-RNA and serum CD4-T cell count after HAV and HBV vaccination, respectively [27, 29, 36]. Similarly, Levin et al. did not observe significant changes in CD4-T cell counts in HIV-infected children receiving a live attenuated varicella vaccine, whereas an increase in CD4-T cell activation was observed by Stanley et al. following tetanus immunization, resulting in an enhanced CD4-T cells susceptibility to both HIV infection and replication [37, 38].
Finally, it is worth noting that no ART failure was observed in the study of Calmy et al., which, as detailed above, reported an increase in HIV RNA levels following vaccination [34]. However, this possibility remains of some concern, since HIV drug resistance mutations can be selected in presence of low-level viremia [39, 40]. Whether or not this risk is also present during transient increases of HIV-RNA in the post-vaccination period deserves further investigations.

## Safety of vaccination in HIV patients

When administering vaccines, as well as any other medication, the development of adverse events may occur. To this regard, inactivated vaccines are generally reported to be well tolerated in HIV patients, with the most frequent side effects being mild and transient local reactions, including pain, redness, swelling, and mild systemic reaction, like headache, fever and general discomfort [24, 30, 36, 41-46]. Although Wallace et al. described a slightly higher rate of systemic adverse reactions in HIV-infected individuals receiving HAV vaccination in comparison with both HIV infected subjects receiving placebo and non-HIV-infected subjects receiving HAV vaccination (37% *vs* 23% *vs* 21%, respectively), no other differences in the incidence of vaccine-related adverse events between HIV-infected and non-HIV-infected subjects have been reported so far [30].

A particular safety concern regarding vaccines administration in HIV patients is the possibility for a live vaccine itself to cause disease. In fact, live-attenuated vaccines might be harmful in patients with severe immunodeficiency. For this reason, international guidelines do not recommend measles vaccination in severely immunosuppressed patients. Anecdotal reports confirm that measles vaccination is potentially dangerous in these patients. For example, an HIV-infected patient who received measles vaccination developed deadly giant-cell pneumonitis one year after. Genomic sequence analysis revealed that the measles virus in lung tissue was similar to vaccine viruses [47]. In addition, in the pre-HAART era several case reports described the development of severe disease after varicella and BCG vaccines in HIV-infected adults [48-50]. Whether or not live vaccines might be used in patients achieving good immunovirological response is a matter of concern. Several recent investigations reported that live vaccines against varicella, zoster and yellow fever were safe in HIV-infected children and adults [37, 46, 51]. However, it should be noted that these studies largely involved those HIV patients without a severe degree of immunodeficiency [37, 46, 51]. Nevertheless, live-attenuated vaccines remains contraindicated in HIV-infected patients with low CD4-T cell count (i.e. < 200/μL) [14].

## Conclusions

Despite the lack of a complete and reliable efficacy data, avoiding the development of preventable diseases through vaccination might be critical in HIV-infected individuals, especially because the immunovirological competence in these patients might be questionable even after viral response and apparently complete immunological recovery. Indeed, these patients should follow tailored vaccination schedules, to prevent diseases that carry a high burden in terms of morbidity and mortality in the HIV population, such as *S. pneumoniae* pneumoniae, influenza, HBV and HPV infection. Vaccines should be administered without waiting for full CD4-T cell count recovery, although immunodeficiency is a possible risk factor for lack of response to vaccination. Finally, inactivated or subunits vaccines should be preferred, since further studies are needed to adequately investigate the safety of live vaccines in HIV-infected patients.

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■ Correspondence: Laura Ambra Nicolini, Infectious Diseases Unit, IRCCS San Martino Hospital, University of Genoa, IRCCS San Martino University Hospital – IST, l.go R. Benzi, 10, 16132 Genoa, Italy - Tel. +39 010 555 4663 - Fax +39 010 5556794 - E-mail: nicolini.la@gmail.com

REVIEW

# Herpes Zoster: the rationale for the introduction of vaccination in Italy

C. PAGANINO, C. ALICINO, C. TRUCCHI, E. ALBANESE, L. STICCHI, G. ICARDI
Department of Health Sciences, Vaccines and Clinical Trials Unit, University of Genova, Italy and IRCCS University Hospital "San Martino", IST National Institute for Cancer Research, Genova, Italy

Key words

Herpes Zoster • Vaccine • Italy

Summary

*Herpes Zoster (HZ) and its main complication, post-herpetic neuralgia (PHN), represent an important public health issue because of their relevant burden within older adult population and the actual suboptimal therapeutic management of the diseases.*
*Incidences of HZ and PHN are comparable all over the world and are closely related with the population age. Epidemiological data collected in Italy about HZ and its complications confirmed the trend registered in North America and Europe. Moreover HZ related burden is exacerbated by a significant economic impact related to both direct and indirect costs.*
*Since 2006 a live, attenuated varicella zoster virus vaccine, that contains VZV Oka strain [Zostavax, Merck & Co., Inc.], was licensed for the prevention of HZ and PHN in adults aged ≥ 60 years. Since 2011, the licensure has been extended to adults between 50 and 59 years. The vaccine has demonstrated a good immunogenicity, efficacy and safety profiles in two pivotal phase III clinical trials and the effectiveness was further confirmed after vaccine licensure. Pharmaco-economic studies concluded that HZ vaccine is cost-effective in most European countries and generally supported the economic value of this vaccination.*
*The vaccine is actually recommended in USA, Canada and several European countries. The opportunity to reduce the burden of these diseases by the recommendation of HZ vaccination have been evaluated and suggested also in our Country and some Regions have been recently introduced the vaccine in their immunization plan. If the good results, already obtained with HZ vaccine in other countries, will be confirmed by these Italian pilot experiences, vaccination programs should be made uniform in all Country in order to ensure an equitable offer of this important preventive tool.*

## Introduction

Herpes zoster is an acute disease, presenting with dermatologic manifestations and neurological pain, caused by the reactivation of the varicella zoster virus (VZV). During primary infection, VZV infects skin nervous endings and remains latent in the sensory ganglia of the spinal dorsal root cord and cranial nerves. Age and immune system depression can favor virus reactivation and leads to the peculiar vesicular rash with unilateral and dermatomeric localization, known as HZ [1].
The most common complication of HZ is constituted by the PHN, a painful syndrome which interests the course of the nerve up to cutaneous dermatome corresponding to the viral site of infection and reactivation [2-4].
PHN commonly occurs with one or more accesses or with paroxysmal pain, burning, allodynia and hyperalgesia and current trends define PHN as a chronic neuropathic resilient pain HZ-related that persists or develops after at least 90 days after wound healing skin and can continue for months or years [5]. As demonstrated in several epidemiological studies, incidence and severity of PHN increase with age; furthermore acute pain and rash severity were recognized as important risk factors for PHN [6-9].
Therapeutic treatments currently available for HZ and PHN are not able to ensure a satisfactory management of the diseases [5]. This therapeutic gap, together with the relevant burden of the diseases, leave unmet medical needs that could be satisfied by vaccination programs.

## Epidemiology

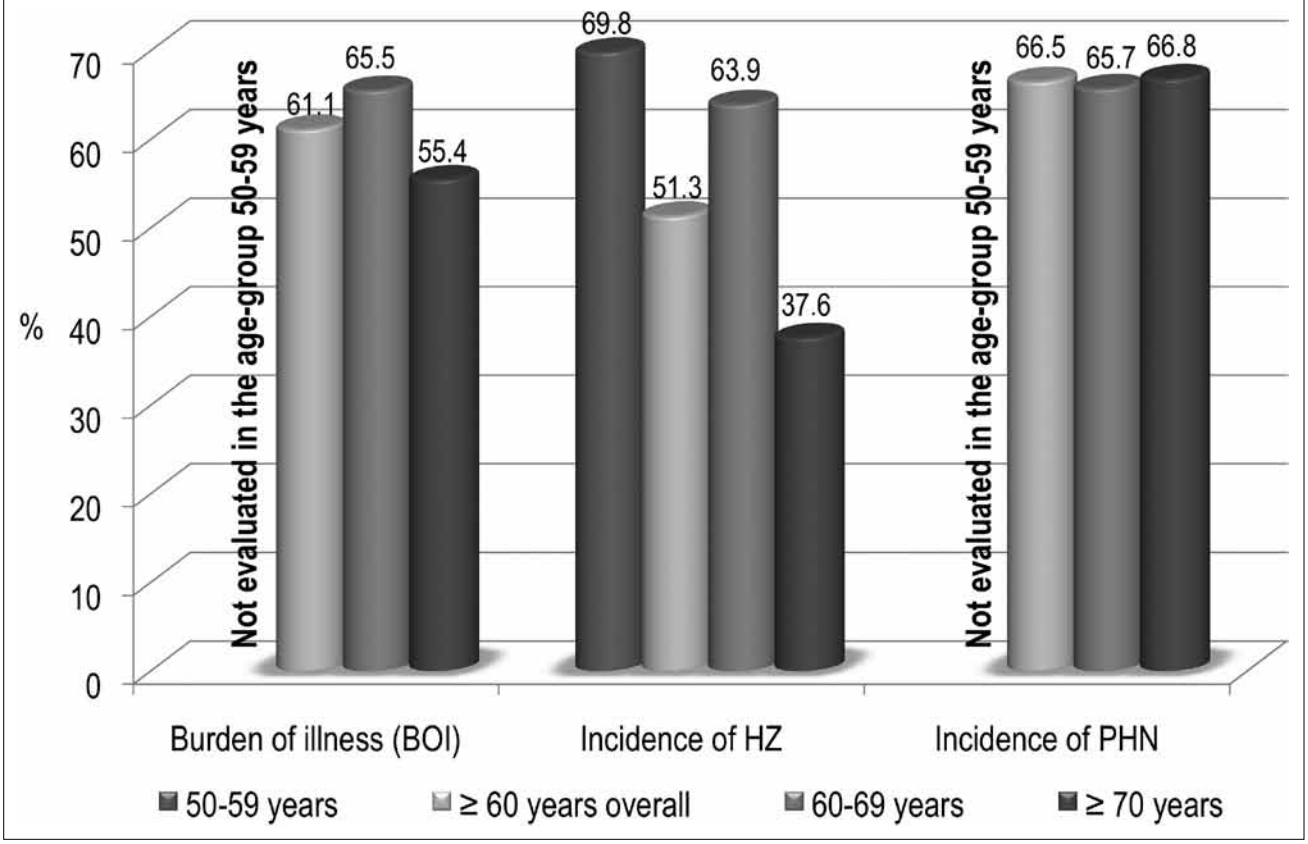
*Incidence of HZ and PHN*. Incidence of HZ is comparable all over the world and is closely related with the population age. A recent systematic review, summarizing incidence rates of HZ reported in 49 studies performed in North America, Europe and Asia, showed that, in these three continents, overall HZ incidence rate ranged between 3 and 5 cases per 1,000 person/years [10]. In these countries the occurrence of HZ is age-dependent and the incidence by age-group shows a similar pattern, with rates of 6-8 cases per 1,000 person/year in the sixth decade and 8-12 per 1,000 person/year in the eighth decade [10].
Similarly, the incidence rate of HZ in Europe is estimated with a frequency of 2-3/1,000 person/year in the adults aged between 20 and 50 years, 5/1,000 in the sixth

decade, 6-7/1,000 from the seventh to the eighth one, and increases up to > 1/100 in 90-year-old people [11].
An Italian study, dealing with the immune-competent adult population older than 50 years, with an observation period of two years (from 2003 to 2005), reported an incidence rate of 6.3 per 1,000 person/year, estimating that, in a population of approximately 24.2 million people aged over 50, at least 153,000 new cases of HZ occur yearly [12]. This Italian research further confirmed that HZ incidence increases with age, therefore older patients have a greater risk of developing HZ [12].
Furthermore these studies clearly demonstrated that incidence of PHN rises with age. In the afore-mentioned systematic review, the risk of developing PHN is estimated between 5% to more than 30% in the adults and in patients with HZ who are 50 or older, the risk of PHN increased to 25-50% [10]. In Europe, adult patients with HZ developed PHN lasting at least 1 month in the 6.5-38% of cases and PHN lasting at least 3 months in the 2.6 to 27% of cases; [13] in Italy it was observed that at least 8% of the adult population with HZ presented a PHN lasting at least 1 month and the 6.2% experienced a PHN lasting at least 3 months. [12] Moreover it was shown that the most important risk factors for the development of PHN are determined by increasing age, female gender and decline of the immune system. [12]
*Hospitalization rates for HZ and PHN in adult patients.* The rates of HZ-related hospitalization, in the 49 countries included in the global systematic review, ranged widely from 2 to 25 per 100,000 person/years in studies examining all age groups. Hospitalization with a primary diagnosis of HZ were about 29-42% of the total HZ-related hospitalizations and these rates increase steeply in adults aged 50 or older [10].
In particular, in the US, HZ-associated hospitalization rates (confirmed with medical records) ranged from 10 per 100,000 in adults aged 60-69 to 65 per 100,000 in adults aged ≥ 80. Similarly, the rate of hospitalization with primary diagnosis of HZ ranged from 13 per 100,000 in adults aged 60-64 to 96 per 100,000 in adults aged ≥ 80 in Australia [10]. In Germany, the rates ranged from 31 per 100,000 in adults aged 60-64 to 100 per 100,000 in adults aged ≥ 80 [10].
Gialloreti et al. analyzed the Italian hospital discharge records related to primary diagnosis of HZ disease and reported an annual hospitalization rate equal to 10.34 per 100,000 person/years within immunocompetent patients older than 50 years. This figure raised to 20.31 per 100,000 when both the primary and secondary diagnosis are considered [12].
*Costs related with HZ e PHN.* In Italy, the annual costs related to the HZ and PHN disease accounted to 41.2 million euros, of which 28.2 million related to direct costs (21.5 million for treatment of acute HZ) and 13 million associated to indirect costs (12.2 in lost productivity related to acute episode of HZ) [12]. These figures corresponded to a direct cost of 166 € for each patient with a HZ episode and 560 € in patients with a PHN episode, furthermore the indirect costs were estimated as € 556 in patients with a HZ episode and € 795 in patients with PHN [12].
In the hospitalized patients the costs, evaluated for a single episode, were approximately € 2,592 ± 1,313 for acute HZ and € 5,400 ± 2,641 for PHN [12]. Similarly, in another study performed in the Piedmont, one of the largest Italian region, the costs related to hospitalization for a single case of HZ were estimated to amount to € 4,082.59 [14].

## Herpes Zoster vaccine

*Efficacy.* Since 2006 a live, attenuated varicella zoster virus vaccine, that contains VZV Oka strain [Zostavax, Merck & Co., Inc.], was licensed for the prevention of HZ and PHN in adults aged ≥ 60 years and in 2008 the Advisory Committee on Immunization Practices (ACIP) recommended its use for the prevention of HZ and its complications in individuals aged ≥ 60 [15]. Since 2011, the vaccine was authorized also for administration in the adults between 50 and 59 by Food and Drug Administration (FDA) [16].
Short-term efficacy of zoster vaccine in adults aged ≥ 50 have been demonstrated in two pivotal clinical trials, including 38,546 subjects aged more than 60 years and 22,439 subjects aged 50-59 years, with respect to three major outcomes: burden of illness determined by HZ, incidence of HZ and incidence of PHN [17, 18].
Figure 1 summarized data about HZ vaccine efficacy among adults aged 50 through 59 and ≥ 60 years. Furthermore, both clinical trials and post-marketing studies demonstrated the optimal safety and tolerability profile of this vaccine [19].
*Duration of protection.* Duration of protection in adults aged ≥ 60 has been studied in two consecutive researches. A persistent vaccine efficacy for HZ and PHN has been indicated in a short-term persistence substudy (STPS), performed within 14,000 subjects. In particular analysis of vaccine efficacy in each year after vaccination for the HZ burden of illness, the incidence of HZ and the incidence of PHN showed a decrease in vaccine efficacy after one year since administration of HZ vaccine, with a further decline thereafter. However, vaccine efficacy remained statistically significant for the incidence of HZ and the HZ burden of illness till five year after HZ vaccine administration [20].
Subsequently, a subgroup of 6,000 subjects were enrolled in a long-persistence study to evaluated the vaccine efficacy up to 11 years after vaccine administration. The results, estimated by a model, revealed that vaccine efficacy decreased over time in the study population compared to modelled control estimates: statistically significant vaccine efficacy for HZ Burden of Illness persisted up to 10 years after vaccination, whereas statistically significant vaccine efficacy for incidence of HZ persisted up to 8 years after vaccination [21].
A recent study, investigating the effect of chronological age on the level of protection provided by HZ vaccine over time with respect to HZ incidence, demonstrated

**Fig. 1.** Efficacy of Herpes Zoster vaccine registered in two phase III clinical trials [17, 18].




that much of the reduction in vaccine efficacy over time since vaccination can be explained by increasing age, responsible for decline of immune response [22].

*Effectiveness.* After the licensure, the on-field effectiveness of HZ vaccine was confirmed by two large studies. A retrospective cohort study, performed among 75,761 vaccinated subjects cohort matched to 227,283 unvaccinated subjects, demonstrated that vaccination was associated with a reduced risk of HZ (hazard ratio = 0.45; 95% CI, 0.42-0.48); this reduction occurred in all age strata and among individuals with chronic diseases [23]. A larger cohort study, performed among more than 700,000 subjects aged > 65 in the period lasting from 2007 to 2009, confirmed these results, demonstrating a vaccine effectiveness, adjusted for age, gender, race, immunosuppression, low income, and comorbidity, of 0.48 (95% CI 0.39-0.56) [24]. This means that an overall vaccine effectiveness (VE) of 48% was demonstrated where VE was calculated as (1 – the adjusted hazard ratio).

*Cost-effectiveness.* A recent systematic review identified and analyzed 15 cost-effectiveness studies of vaccination against HZ and PHN performed in North America and Europe [25]. Most studies conducted in Europe and Canada concluded that HZ vaccine is likely to be cost-effective and generally supported the economic value of this vaccination. Divergences in results among studies were largely attributable by authors to differing assumptions regarding duration of vaccine protection and a loss in quality of life associated with HZ and to a larger extent, PHN. Moreover, vaccine efficacy against PHN, age at vaccination, and vaccine cost strongly influenced the results [25].

A pharmaco-economic evaluation performed in Italy confirmed that vaccination program against HZ and PHN within subjects aged 60-79 years is cost-effective from both societal and third-payer standpoints in the Italian scenario [19].

## Conclusions

HZ and its main complication, PHN, represent an important public health issue because of their relevant burden within older adult population and the actual suboptimal therapeutic management of the diseases.

The licensure since 2006 of a live attenuated HZ vaccine in adults aged more than 60 years, extended since 2011 in adults aged 50-59 years, had stimulated the interest by the public health to evaluate the introduction of HZ vaccination in these categories in order to reduce the healthcare and economic burden associated with HZ.

The vaccine is actually recommended in USA and Canada in patients ≥ 60 years since 2006 and 2010, respectively. In Europe, vaccination is recommended in several countries (i.e. Germany, United Kingdom, Sweden, Austria, France) according to age-based strategies [19].

In Italy, available epidemiological and economic data about HZ and its complications are superimposable with

similar data collected in North America and Europe. For these reasons, the opportunity to reduce the burden of these diseases by the recommendation of HZ vaccination have been evaluated and suggested also in our Country [19].

During 2014, some Italian regions, such as Liguria and Puglia, established to introduce HZ vaccination in the regional immunization plan by the active and free offer of the vaccine to specific age-group.

The administration of HZ vaccine within public health strategy in these Regions offers the opportunity to assess on-field its safety and tolerability profile and, importantly, to evaluate the impact of vaccination on healthcare services.

If the good results, already obtained with HZ vaccine in other countries, will be confirmed by these Italian pilot experiences, vaccination programs should be made uniform in all Country in order to ensure an equitable offer of this important preventive tool.

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■ Correspondence: Cristiano Alicino, Department of Health Sciences, University of Genova and Hygiene and Infection Control Unit, IRCCS AOU San Martino-IST teaching Hospital, Largo R. Benzi 10, 16132 Genoa, Italy - Tel. +39 010 5552033 - E-mail: cristiano.alicino@unige.it

REVIEW

# Influenza vaccination in the elderly: why are the overall benefits still hotly debated?

C. TRUCCHI, C. PAGANINO, A. ORSI, D. DE FLORENTIIS, F. ANSALDI
Department of Health Sciences, University of Genoa, Italy and IRCCS University Hospital San Martino, IST National Institute for Cancer Research, Genoa, Italy

Key words

Influenza vaccine • Vaccine efficacy • Vaccine effectiveness

Summary

*The exact magnitude of the benefit of influenza vaccine among elderly individuals is subject of considerable debated. Existing vaccine effectiveness estimates come mostly from observational studies, which may be biased because of difficulties in identifying and adjusting for confounders. In this paper, we examine the potential sources of bias in observational studies of influenza vaccine effectiveness in the elderly and we discuss available evidence regarding the efficacy and effectiveness of licensed influenza vaccines. Although several methodological criticisms among the available analyses on seasonal vaccines for elderly were identified, overall seasonal influenza vaccines showed relevant efficacy/effectiveness in reducing the risk of influenza and its complications in the elderly, considering different measure of outcome.*

## Introduction

Influenza infection is associated with considerable yearly morbidity and subjects aged ≥ 65 years are among those at highest risk of serious outcomes [1, 2]. Annual influenza vaccination, that is considered the most effective strategy to prevent influenza by the World Health Organization, is recommended for elderly in many developed countries [3]. However, the exact magnitude of the benefit of the current immunization strategy among older adults is a subject of considerable debate [4-10]. Most estimates of the influenza vaccine effectiveness (IVE) are based on studies using different designs and outcomes, which provided a wide range of IVE estimates in the elderly (adults ≥ 65 years-old) [10, 11]. Furthermore, as most of the IVE studies are observational, they are susceptible to bias. Confounding factors such as comorbidities or functional status can alter the estimates and different methods to adjust for these confounding factors have been suggested [5, 12]. The present study discusses available epidemiological studies estimating IVE and criticisms in the evaluation of influenza vaccine efficacy and effectiveness, defined as the relative reduction in influenza risk after vaccination as established by a randomized placebo-controlled clinical trial (RCT) and the relative reduction in influenza risk in vaccinated individuals in observational studies that used medically attended, laboratory-confirmed influenza as the primary outcome of interest, respectively [13].

## Criticisms in the evaluation of influenza vaccine efficacy and effectiveness

### Which epidemiological study can estimate influenza vaccine effectiveness?

Not many RCTs on the influenza vaccine efficacy in older adults have been conducted, because of ethical issues concerning interventions that are recommended [14]. In the last two decades, the only large RCT of inactivated influenza vaccine in adults aged ≥ 60 years was conducted during a single season and it was limited to healthy subjects. This RCT demonstrated a reduction in risk of serologically confirmed uncomplicated influenza infection in participants 60-69 years-old, with an estimated efficacy for prevention of serologically-confirmed influenza in symptomatic subjects of 58%, but no strong conclusions about the IVE could be drawn about those ≥ 70 years-old because this RCT was inadequately powered to examine the efficacy of the vaccine in this age group [15]. Moreover, the efficacy evidence in healthy subjects 60-69 years-old may not apply to fragile elderly ≥ 70 years-old because advanced age and the comorbidities are associated with an increased risk of complications and the weakening of the immune system [16-22]. Without satisfactory data from RCTs, estimates of IVE among older subjects result from observational studies, typically from retrospective cohort studies, which may be biased [12, 23]. Many observational studies have compared the risk of hospitalization pneumonia-related and all-cause mortality in vaccinated and unvaccinated elderly during influenza season and have reported significant reductions in risk for vaccinated subjects, with reductions of 50% for all-cause mortality and of 27-33% for pneumonia and influenza hospitalization [24-41]. Some authors interpreted

these results as evidence that influenza vaccine substantially reduces the risk of death and hospitalization in the elderly [11, 42-46]. Nevertheless some studies, as the review published in 2007 by Simonsen et al. [9], state that there is evidence for bias in estimated risk reductions for vaccinated versus unvaccinated elderly in available observational studies, especially those not using laboratory-confirmation as outcome, that is considered the gold standard. Simonsen et al. [9] observed that the finding of reductions ≥ 50% in all-cause mortality for vaccinated elderly during influenza season is implausible, considering that influenza accounts for a maximum of 10% of all deaths during influenza season [47] and, therefore, influenza vaccine could at most prevent 10% of deaths, even if the vaccine efficacy was 100% in the elderly. Furthermore, estimated risk reductions for vaccinated elderly are not specific to seasons with a matching between the circulating and vaccine influenza strains. Nordin et al. reported large reductions in risk of death and hospitalization in vaccinated elderly in the 1997-1998 influenza [33], characterized by a mismatch and during which a RCT found no vaccine effect in healthy adult workers [48]. Moreover, the greatest apparent vaccine benefit has been observed before influenza season, when no effect is expected [5]. Two further studies [5, 47] are of particular interest. In 2005 Simonsen et al. conducted an ecologic study [47] and reported that, despite substantial increases in vaccine coverage (VC) from about 15% in 1980 to ≥ 65% by 2001 in elderly, rates of winter excess morbidity and mortality have not declined during this period. If the estimated mortality reduction of 50% by influenza vaccine is real, the observed excess mortality rate should have decreased with increasing VC [12]. Second, a large cohort study [5] assessed the risk of death and hospitalization in vaccinated and unvaccinated elderly in both influenza and non-influenza periods. The study confirmed that vaccinated subjects 60-69 years-old were at lower risk (44% for all-cause death) during influenza season, but revealed a larger risk reduction before the onset of influenza season (61% for all-cause death), when the IVE is expected to be 0%. Therefore this finding suggests the presence of confounding and any estimated difference in risk between vaccinated and unvaccinated elderly during this period is related to bias. Similar bias were found in pre-influenza estimates of the association between vaccination and other outcomes, including hospitalizations for pneumonia or influenza. Finally, available observational studies about IVE frequently use data from databases, such as the General Practitioners Research database, health care utilization data systems, or those kept by some health maintenance organizations in the United States [12]. In 2005 Schneeweiss and Avorn published a review about general methodological issues that arise using these databases in health research, such as data inaccuracies and residual confounding, but they didn't discuss methodological criticism specific to influenza vaccination [49].

The "case-coverage" or "case-cohort" method is another type of study to estimate IVE. In this case, vaccination rates among cases are compared with those in a similar cohort (which may include individuals who develop cases) over a defined period of time [50]. This method has been used in a study published in 2008 by Szilagyi et al. that evaluated IVE among children 6-59 months of age during 2 influenza seasons [51]. The authors concluded that this type of study design is "inefficient and may insufficiently account for important factors, such as propensity to seek care" and that it has "important limitations in being able to annually assess IVE".

In recent years, the test-negative design, that is an analogous to the indirect cohort study [50], has arisen as the preferred method for estimating IVE in observational studies [52]. This type of study design consider as study subjects all persons who seek care for an acute respiratory illness (ARI) and who are tested for influenza infection. IVE is estimated from the ratio of the odds of vaccination among subjects testing positive for influenza to the odds of vaccination among subjects testing negative. The main advantage of this study design is that it allows removing differences in health care-seeking behavior between vaccinated and unvaccinated subjects in the study design phase.

### Which factor may interfere with vaccine effectiveness estimates?

Vaccine effectiveness can be measured using different endpoints, each of which has advantages and disadvantages [53]. In the recent past, the most frequently considered endpoints include the incidence of clinically defined influenza-like illness (ILI) and laboratory-confirmed influenza. The methods used to the laboratory confirmation include viral culture, serologic rises between pre and post influenza season samples and molecular methods [53]. Unfortunately, none of these are both specific and sensitive methods. Typically influenza presents with the acute onset of fever, myalgia and cough [54]. The Centers for Disease Control and Prevention (CDC) defined ILI as fever with either cough or sore throat for research purposes [55]. This CDC-ILI definition has high positive predictive value in young adults (86.8%) [56] during periods of high influenza activity, but it is much lower in older adults, who frequently don't have fever and other manifestations of influenza [57, 58]. Furthermore, vaccine impact on severe outcomes such as hospitalization and death may be difficult to measure because of the large sample sizes needed to accurately estimate rare events like these [59]. Conventionally, culture has been considered the gold-standard for the diagnosis of influenza [53]. Nevertheless, viral titers in the respiratory secretions of older adults are generally lower than those of younger adults and children, reducing the sensitivity of culture in this age group when compared with serology and polymerase chain reaction (PCR) [60]. Serology is another common but not sensitive endpoint for estimating IVE. A positive case of influenza is usually defined as a ≥ 4-fold rise in antibody titers between the pre- and post-season serology [53]. Some authors have suggested that this endpoint might overestimate the efficacy of vaccine because of the "antibody ceiling" phenomena, that could be explained as follows: once antibody titres have increased in response to the vaccine, they could go no higher in response to infection [61]. Furthermore, the association of immune

correlates of vaccine protection with efficacy against disease is not always dependable endpoint [62], particularly weak in young children, the elderly and immunocompromised, i.e. target groups that may respond least well to vaccination [63]. Use of real-time PCR (RT-PCR) with appropriately designed primers and probes for detecting influenza infection has now become the gold standard ant it should be the primary end point used in future efficacy studies [64]. The test is highly sensitive, so much so that concerns has been raised that it might detect subclinical infections that are not clinically relevant [64]. Isolation in cell culture must still be used in those RT-PCR positive to further characterize the viruses, but use it alone as an endpoint could result in missed cases and biased results [64, 65].

## Potential bias in estimates of influenza vaccine effectiveness

The risk of selection bias in observational studies estimating IVE has been discussed in many available studies [4-6, 8, 9, 12].

Although universally recommended for old subjects, acceptance of influenza vaccine is voluntary and a preferential receipt of vaccine by motivated relatively healthy elderly and a selective underuse by frail elderly were demonstrated [5-7, 9, 12]. Healthy adherer bias may be more noticeable for influenza vaccine than other type of exposures for several reasons. First, limited availability of vaccine (late autumn and winter) may limit the chance for vaccination. Several studies demonstrated that elderly subjects who have a car or can walk to their health care provider's office [66], live with others who can assist them [67], or have fewer functional limitations [6] are more prone to be immunized. A case-control study of all-cause mortality conducted in 824 elderly during influenza season found that severe functional limitation, in particular requiring assistance for bathing, was associated with a 13-fold increased risk of death and a 52% decreased likelihood of vaccination [6]. Therefore, disability appears as a contributing factor in the decision to receive or resist vaccination near the end of life. A further factor that may aggravate bias is the use of all-cause death as a study outcome, because it is nonspecific and so expected vaccine effects are small and thus difficult to distinguish from confounding, which may be large [68]. To differentiate vaccine effects from bias, Fireman et al. has proposed a "difference in differences" approaches [4]: if the flu vaccine really does prevent deaths, then in a large population there should be a detectable difference between: (i) the difference in the odds of prior vaccination decedents and survivors that is observed on days when influenza is circulating and (ii) the difference in the odds of prior vaccination between decedents and survivors that would be expected on the same calendar dates if influenza were not circulating. The implementation of the "difference in differences" approach consisted of tracing the trajectory of the bias over time and comparing the vaccination-mortality association inside flu season with that outside flu season. Estimated VE against all-cause mortality during 1996-2005 flu seasons was 4.6% (95% CI: 0.7 – 8.3). Although this estimate may seem unsatisfactory, it amounts t approximately 47% of a plausible target: the rise in mortality that would have occurred during flu season had none of the elderly been vaccinated.

## Available estimates of influenza vaccine efficacy and effectiveness against lab-confirmed influenza in adults aged 50 years and older obtained by meta-analyses

A considerable body of evidence has been produced on influenza vaccines for different types of virus strains and various populations and settings [69]. Between 1995 and 2011 numerous meta-analyses evaluating the benefits and harms of influenza vaccines mainly in adults and elderly have been published, as an effort to integrate this evidence [13, 44, 70-77]. In 2012 Osterholm et al. [13] published a meta-analysis of RCTs and observational studies that assesses the highest quality evidence about the efficacy and effectiveness of licensed influenza vaccines in the USA using RT-PCR or viral culture to confirm influenza infections. Vaccine efficacy was defined as "the relative reduction in influenza risk after vaccination as established by a RCT". Vaccine effectiveness was defined as "the relative reduction in influenza risk in vaccinated individuals in observational studies (case-control, case-cohort and prospective cohort studies) that used medically attended, laboratory-confirmed influenza as the primary outcome of interest" [50]. Laboratory-confirmed influenza was defined as RT-PCR-confirmed, the preferred diagnostic test for influenza because characterized by high sensitivity and low probability of false positive [78], or culture-confirmed influenza. Trivalent influenza vaccine (TIV) efficacy and effectiveness studies that considered serology endpoints to diagnose influenza were excluded because of bias in case detection in immunized subjects [64, 79]. For all the considered studies, efficacy and effectiveness were evaluated as statistically significant if the 95% CI did not cross 0.

### Efficacy

None of the evaluated RCTs assessing TIV efficacy exclusively considered subjects aged ≥ 65 years-old and this is attributable to ethical issues. For LAIV, the only RCT conducted in adults aged ≥ 60 years-old reported significant overall efficacy (42%, 95% CI: 21-57), but estimated efficacy was lower in subjects aged 60-69 years-old (31%) and higher in those aged ≥ 70 years-old (57%) [80].

### Effectiveness

Several observational studies about influenza vaccines effectiveness have been conducted [13], especially on TIV. Main recent evidences are following described. Since 2007 the European Centre for Disease Prevention and Control (ECDC) has promoted I-MOVE (Influenza Monitoring Vaccine Effectiveness), a network to moni-

tor seasonal and pandemic IVE in the European Union (EU) and European Economic Area (EEA) [81]. Initial phase of I-MOVE network include five case-control and two cohort studies evaluating IVE in 2008-2009 season. The studies were piloted in the network of active General Practinioners (GP)-based influenza sentinel surveillance systems and assessed IVE against laboratory confirmed influenza in community-dwelling elderly [82]. The estimated crude IVE in the pooled analysis was 55.1% (95% CI: 27.8-72.1%). The overall IVE adjusted for study, age, sex, presence of chronic conditions, previous hospitalizations, smoking history, functional status, and previous influenza vaccination was 59.1% (95% CI: 15.3-80.3%). The adjusted IVE in subjects 65-74 year-olds was 65.4% (95% CI: 15.6-85.8%) and 59.6% (95%: CI: -72.6-90.6%) in the age-group of ≥ 75 years. Spain participated in I-MOVE project with a case-control study using two different control groups. IVE against laboratory-confirmed influenza in elderly ≥ 65 years was also estimated by Savalescu et al. using the screening method [83]. Both designs (case-control and screening method) were carried out in the frame of the Spanish Influenza Sentinel Surveillance System (SISSS) in 2008-2009 season. Participating sentinel GPs of the framework swabbed all patients who were attended for ILI. Study cases were defined as "ILI patients swabbed and laboratory confirmed for influenza by RT-PCR or culture". The first control group included ILI cases testing negative for influenza (test-negative controls) and the second one comprised patients not having had respiratory symptoms since the beginning of the season (non-ILI controls). The crude estimated IVE was 86% (95% CI: 43-98) and the IVE adjusted for chronic conditions, previous hospitalizations, functional status, smoking, previous influenza and pneumococcal vaccination was 79% (95% CI: -26-96). In the same period Talbot et al. conducted a prospective observational study, published in 2012 [53]. Patients aged ≥ 50 years with respiratory symptoms or fever hospitalized in Davidson County, TN (Nashville) during three influenza seasons (2006-2007, 2007-2008 and 2008-2009) were enrolled and influenza vaccination status was compared in those with and without laboratory-confirmed influenza by RT-PCR to estimate IVE for the prevention of hospitalization. For each of the three evaluated seasons, unadjusted annual estimates were 59.4% (95% CI: -26.7-87%), 61.8% (95% CI: -29.4%-88.7%) and 81.8% (95% CI: 34.8-94.9%), respectively. With propensity-score adjustment, overall IVE for the three influenza seasons was 61.2% (95% CI: 17.5-81.8%).

## Available estimates of TIV efficacy and effectiveness against influenza in the elderly obtained by umbrella review

Given that published meta-analyses on influenza vaccine efficacy and effectiveness evaluated different types of vaccines, different age-groups and used different stratified analyses and study selection criteria, it's difficult to obtain a clear picture of vaccine benefits examining single meta-analyses [69]. Consequently, in 2012 Manzoli et al. conducted an umbrella review, i.e. an over-arching evaluation of all recent meta-analyses on vaccine efficacy and effectiveness (Fig. 1).

Four meta-analyses including both RCTs and observational studies on TIV conducted in the elderly were discussed [13, 44, 76, 84].

Two meta-analyses estimated vaccine efficacy/effectiveness against laboratory-confirmed cases of influenza (LCC) [13, 84]. Influenza vaccine efficacy estimated by RCTs was 58% (95% CI: 34%-73%), while the estimates of IVE from cohort studies varied from 41% (95% CI: -15%-70%) in the Jefferson et al. meta-analysis, that included only LCC based on serology, to 63% (95% CI: 28%-81%) in the Osterholm et al. meta-analysis, that evaluated a more specific outcome (RT-PCR or culture-confirmed influenza infections only). Concerning clinically confirmed cases (CCC), all considered reviews demonstrated that influenza vaccine confer significant protection. The four evaluated RCTs estimated a summary efficacy of 41%, while the meta-analyses of cohort studies showed an overall IVE ranging from 56% [44] to 24% [84].

Three meta-analyses evaluated also other outcomes [44, 76, 84], demonstrating that TIV was significantly better than placebo in preventing hospitalizations due to influenza or pneumonia. However the estimates varied, ranging from 48% [44] to 27% [84].

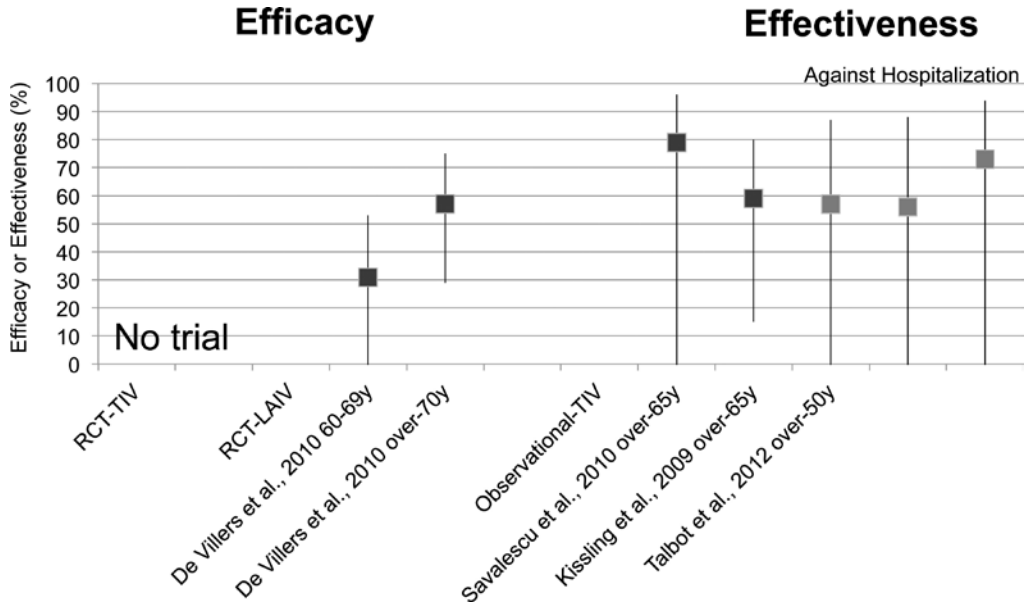
Three meta-analyses considered the outcome mortality [44, 76, 84]. Unexpectedly, the estimates of IVE in preventing mortality due to influenza or pneumonia were similar to those of all-cause mortality [47].

Combining observational studies, all meta-analyses demonstrated a significant reduction of deaths for all causes, with IVE ranging from 68% to 47%.

The effect of vaccination is expected to be higher in case of a good antigenic matching between the circulating and the vaccine strains [85]. However, Gross et al. observed a significant IVE even in seasons in which mismatching was demonstrated [44]. Jefferson et al. [84] observed that IVE in preventing hospitalization due to influenza or pneumonia and all cause mortality was substantially higher in seasons with good matching. Nevertheless, in 2010 Dean et al. published a cluster randomized trial, which demonstrated that influenza vaccine can be effective against disease and severe outcomes despite incomplete vaccine match [86].

Manzoli et al. summarized that Gross et al. [44] and Vu et al. [76] observed that influenza vaccines are effective in preventing influenza cases, hospitalizations and deaths in the elderly, while Osterholm et al. stated that "evidence for protection in adults aged 65 years or older is lacking" [13]. However, the conclusions by Osterholm et al. could be due to the choice of restrictive inclusion criteria [87]. Jefferson et al. stated that "the available evidence is of poor quality and provides no guidance regarding the safety, efficacy or effectiveness of influenza vaccines for people aged 65 years or older," but these observation may be influenced by the evidence of potential biases [84].

**Fig. 1.** Available estimates of influenza vaccine efficacy and effectiveness against lab-confirmed influenza in adults aged 50 years and older obtained by meta-analyses.




## Conclusions

The overall evidences suggest that most influenza vaccines confer relevant protection against naturally acquired infection also in the elderly, who are at increased risk for influenza and complications due to influenza infection [53, 69, 88]. However, the assessment of vaccine benefits is still affected by considerable methodological challenges [88]. There is evidence for the presence of bias in available observational studies estimating the IVE in the elderly and that current adjustment methods could not adequately control it [12]. Some of the outcomes evaluated in the comprehensive umbrella review by Manzoli et al. seem to be surprising when compared, i.e. the large impact on all-cause mortality in the elderly as opposed to far more modest effects against CCC [69]. However, Manzoli et al. concluded that "although several discrepancies among meta-analyses on seasonal vaccines for elderly were identified, most seasonal influenza vaccines show statistically significant efficacy/effectiveness, the magnitude of which, however, largely varied" [69]. The conduct of adequately powered publicly-funded RCTs on elderly could be a solution, but this would be also an expensive and an ethically complex proposal, because the use of influenza vaccines is recommended worldwide from several years [69, 88] and cost-effectiveness issues have to be properly re-assessed in times of economic recession [89].

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■ Correspondence: Filippo Ansaldi, largo R. Benzi 10, 16132 Genoa, Italy - Tel. +39 010 5552333 - E-mail:filippo.ansaldi@unige.it

REVIEW

# Decennial diphtheria-tetanus adult boosters: are they really necessary?

C. TRUCCHI[1], G. ZOPPI[2]
[1] Department of Health Sciences, University of Genova, Italy; [2] Department of Prevention, OU Hygiene and Public Health, LHU 4 "Chiavarese", Liguria Region, Italy

Key words

Diphtheria-tetanus • Vaccine • Booster

Summary

*Available epidemiological data shows that an average number of 59 cases of tetanus per year are still reported in Italy. Most of cases (80.2%) occur in subjects > 64 years-old. Furthermore, the proportion of females among subjects ≥ 65 years-old is significantly higher than males (87.7% vs. 64.4%, p < 0.0001).*
*Seroprevalence data show that the percentage of subjects with protective tetanus antibody levels (> 0.1 IU/ml) decreases with increasing age. Most people aged ≥ 65 years are unprotected. The antibody levels are higher in males than females (p < 0.001) in subjects > 25 years-old.*
*Conversely, extensive childhood immunization and adequate boosting vaccination of adults led to the near-elimination of diphtheria in Western countries.*
*The current Italian National Immunization Prevention Plan 2012-2014 recommends the administration of a primary vaccine course in the first year of life and booster at the preschool age, in adolescents and in adults every 10 years. Nevertheless, the need for decennial booster doses is debated by some experts, who state that the best time to offer a single dose of vaccine against tetanus and diphtheria is the age of 50, since low levels of antibody titers are observed.*
*Considering the availability of combined vaccines against diphtheria, tetanus and pertussis (DTaP or dTaP), and the increasing incidence of pertussis in infants, who are at highest risk of serious complications, in adolescents and in adults, some countries have introduced decennial dTaP in the adults immunization schedule. It is desirable that this recommendation is also introduced in the future Italian Immunization Prevention Plan.*
*The present review overviews the epidemiological data and the immunization strategies against tetanus, diphtheria and pertussis in Italy, discussing the rationale not only of decennial dT booster but also of the dTaP booster.*

## Introduction

Tetanus and diphtheria are two serious infectious diseases caused by powerful exotoxins produced by *Clostridium tetani* and *Corynebacterium diphtheriae* respectively, with often-fatal outcome.
*C. tetani* is an anaerobic gram-positive bacteria, that may develop a terminal spore. The spores are widely distributed in soil, in the inanimate environment and in animal intestinal tract and feces. Tetanus occurs by penetration of spores through contaminated wounds, lacerations and abrasions. Deep wounds, with lacerated and bruised margins, devitalized tissue, contaminated with soil, are at high risk of tetanus. Toxins disseminate via blood and lymphatics and interfere with release of neurotransmitters [1]. Tetanus is infectious, but not contagious and natural infection does not confer lifelong immunity. Unlike person-to-person transmissible diseases, high vaccination coverage (VC) in the pediatric age does not provide herd immunity. Furthermore, it is almost impossible to eliminate the disease because of the widespread presence of tetanus spores in the environment. Consequently, inadequately immunized subjects are potentially at risk [2].
Clinically, it is characterized by generalized rigidity and convulsive spasms of skeletal muscle and by autonomic nervous system disfunctions, after an average incubation period of 7 days [3].
*C. diphtheriae* is a gram-positive, uncapsulated bacillus, most often transmitted via the aerosol route. Human asymptomatic carriers are a major source of infection. Whereas toxigenic strains of *C. diphtheriae* most frequently cause pharyngeal diphtheria, systemic toxicity, myocarditis and polyneuropathy, non-toxigenic strains usually cause cutaneous disease. The average incubation period of respiratory diphtheria is 2-5 days. Distinctive pathologic findings of severe respiratory diphtheria include mucosal ulcers with a pseudomembranous coating, which may extent from the pharynx into bronchial airways and may result in fatal airway obstruction. Cutaneous diphtheria is commonly a secondary infection that follows a primary skin lesion due to trauma, allergy or autoimmunity [4, 5].
The present review overviews the epidemiological data and the immunization strategies against tetanus, diphtheria and pertussis in Italy, discussing the rationale not only of decennial dT booster but also of the dTaP booster.

## Epidemiology of tetanus and diphtheria in Italy

### Tetanus

From the second half of 1950s to the mid of 1960s 722 cases of tetanus (1.4 cases per 100,000 population) were notified yearly in Italy. Up to the half of 1970s the number of cases considerably decreased, as a consequence of the introduction of universal childhood immunization during 1960s. Subsequently, the decrease of the cases occurred more slowly, reaching the all-time low of 65 cases in 1991. From 1992 to 2000 the number of cases remained stable, with a mean of 102 cases per year (0.2 cases per 100,000 population). The last case of neonatal tetanus dates back to 1982. The reduction in the incidence observed between the 1970s and 1990s was evident in all age groups. During the considered period, the highest incidence rate was observed in subjects ≥ 65 years-old. The greatest reduction (20-fold) in incidence occurred in the 15-24 years age group. Conversely, the incidence in the elderly decreased only by a half. Furthermore, the percentage of cases ≥ 65 years of age increased from 40% in the 1970s to 70% in the 1990s. These observations have been confirmed by the analysis of the median age of cases, which increased from 58 years in the 1970s to 63 years in the 1980s and 71 years in the 1990s. Analyzing epidemiological data by gender, in the 1990s, rates were higher in woman than in male among subjects ≥ 65 years. This is probably due to the fact that in this age group male counterparts were vaccinated as military recruits or because of job-related risks. As incidence rate, the case-fatality also decreased from 64% in the 1970s to 40% in the 1990s [2].

Available data about the decade 2001-2010 shows that an average number of 59 cases (range: 46-71) per year (1 per 1,000,000 population) are still reported in Italy. Despite high VC were achieved, Italy accounts for most cases reported in the European Union (EU) [6] and tetanus incidence in Italy is about 10 times higher than the average incidence reported in the USA and Australia [7, 8]. As observed in previous years and in other developed countries [9], most of cases (80.2%) occur in subjects > 64 years-old, with an incidence rate equal to 4.1 per 1,000,000 population. The estimated incidence in Italy in the decade 2001-2010 in female is 5.2 per 1,000,000 population (68% of cases), that is over three-fold higher than in male (1.4 per 1,000,000 population). The estimated incidence in Italy in the decade 2001-2010 in female is 5.2 per 1,000,000 population (68% of cases), that is over three-fold higher than in male (1.4 per 1,000,000 population). Furthermore, the proportion of female among subjects ≥ 65 years-old was significantly higher than males (87.7% *vs.* 64.4%, $p < 0.0001$). The average annual hospitalization rate of 1.6 per 1,000,000 population, with a median length of stay of 25 days. 79.8% of patients was > 64 years-old and 69% involved female. The estimated case fatality ratio was 16.5%. National mortality data were available for the years 2001-2003 and 2006-2010. 169 deaths were reported, with a mean annual number of 21 (range: 17-27). Seroprevalence data about the same period are also available and show that the percentage of subjects with protective tetanus antibody levels (> 0.1 IU/ml) decreases with increasing age from 87% (95% CI: 84.1-89.5) in the age group 15-24 years to 43.4% (95% CI: 38.6-48.3), 26.6% (95% CI: 21.4-32.2), 27.9% (95% CI: 22.3-33.9) and 17.1% (95% CI: 6.6-33.6) in the age groups 45-64, 65-74, 75-84 and ≥ 85 years, respectively. Therefore, most people aged ≥ 65 years are unprotected and this is probably due to inadequate VC. Furthermore, most elderly people probably never received a primary vaccination course. Low antibody levels observed in young adults suggest poor compliance with booster recommendations. The observed antibody levels were higher in males than females ($p < 0.001$) from age 25 years. This is probably due to the fact that males had more opportunities for being vaccinated compared to female, such as compulsory military service or work. Then, despite the availability of safe and effective vaccines, too many cases and deaths still occur, especially among older adults [10].

### Diphtheria

Before the introduction of universal vaccination with aluminum-containing toxoids in 1939 in Italy, the disease was a widespread disease and major cause of death, especially in children. The number of reported cases per year and deaths until 1940 were 20-30,000 and 1,500, respectively. In the 1950s and 1960s, the number of reported cases reached several thousands per year. Then, between 1973 and 1982 the number of cases fell to a few per year. Since then the disease has become exceptional: only 5 cases of diphtheria were registered between 1990 and 1998, one of which was imported. From 1999 to 2006 no case has been reported. Extensive childhood immunization and adequate boosting vaccination of adults led to the near-elimination of diphtheria in Western countries [11, 12]. Data obtained from a seroprevalence study conducted in eight Italian cities from June 1993 to June 1995, demonstrated the progressive reduction in antibody titers as age increases. The percentage of subjects with unprotective antitoxin concentrations progressively increased from 7.2% in the 1-10 years age group to 33.4% in subjects aged > 60 years. This is related to the fact that, at that time, no further booster was recommended after the childhood immunization course and it suggests that the immunological memory declines with age [13].

## Prevention of tetanus and diphtheria

### a) The available vaccines

In the 1920s, Ramon at the Institut Pasteur developed a method for inactivating tetanus and diphtheria toxins, which led to the development of tetanus and diphtheria toxoids, which were nontoxic but highly immunogenic [1, 5]. Tetanus and diphtheria toxoids are produced from the cell-free purified toxins extracted from the strain of *C. diphtheriae* and from *C. tetani*. They are treated with

formaldehyde to convert toxin into toxoid and it is then adsorbed onto an aluminum salt to improve its immunogenicity [1, 5, 14].
Tetanus toxoid is available as a single-antigen preparation, combined with diphtheria toxoid as pediatric diphtheria-tetanus toxoid (DT) or reduced tetanus-diphtheria (Td) formulated for adolescents and adults, and with both diphtheria toxoid and acellular pertussis vaccine as DTaP or Tdap. DTaP replaced DTP (diphtheria and tetanus toxoids and whole-cell pertussis vaccine) in 1997 [3]. Tetanus toxoid is also available as combined products diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (DTaP-IPV), diphtheria/tetanus/acellular pertussis/hepatitis B/inactivated polio vaccine (DTaP-HepB-IPV) and diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/*Haemophilus influenzae* type b (DTaP-IPV-Hib) [1, 5, 14].
Seroprotection rate evaluated up to 10 years after booster vaccination of children at pre-school age demonstrated that almost all subjects achieve antitoxin levels against both diphtheria and tetanus considerably greater than the protective level of 0.1 IU/ml. Nevertheless, antitoxin levels decrease with time in adulthood [15].

### b) Strategies for preventing diphtheria, tetanus (and whooping cough) in Italy

Tetanus toxoid vaccine was introduced in 1938 as compulsory vaccine only for military personnel. In 1963 it became compulsory also for children two-year-old and for specific work categories and in 1968 the vaccine is administered during the first year of life [10].
Immunization with diphtheria toxoid is available from 1929 and it has been compulsory for all newborns since 1939. Since 1969, diphtheria vaccine is administered combined with tetanus toxoid. Furthermore all newborn receive a primary course that includes three doses since 1981 [13].
The current Italian National Immunization Prevention Plan 2012-2014 recommends the administration of the vaccine against tetanus and diphtheria (in association with the vaccine against polio, whooping cough, hepatitis B and *Haemophilus influenzae* type b) in the first year of life (3 doses) [16]. In the preschool age a booster of diphtheria, tetanus, pertussis and polio (DTP-IPV) is recommended and a second booster with the adult formulation (dTpa) is timetabled in adolescent age (11-18 years). In adults dT booster doses are recommended every 10 years, even if it is recommended that if the adult has never been vaccinated for DT one of three doses of vaccine should also contain antigens for pertussis. It is recommended that adults with unknown dT immunization history begin or complete the primary course. The adult primary course included two doses of dT and a third dose with dTap vaccine. The following booster should be administered every 10 years after the primary course and at least one of the booster doses should be replaced by a dTap dose.
Booster recommendations vary among countries, taking into account the seroepidemiological data of tetanus and diphtheria and the incidence in different age groups [9, 17-20]. Nevertheless, the need for decennial booster doses is debated by some experts [21-25]. Some authors stated that the interval between adult boosters could be wider, maybe of 20 years [25]. Furthermore, according to some experts, the best time to verify tetanus immunization status and to offer a single Td dose is the age of 50 [26]. This strategy could be appropriate even in Italy, considering that the lowest level of antibody titers was found in adults ≥ 45 years of age [10]. Surely, strategies to improve vaccine uptake in this age group should be implemented.

#### *Post-exposure prophylaxis for tetanus*

Appropriate wound management in the Emergency Departments is also essential for preventing tetanus [27].
Wound management requires the consideration of the need for (i) passive immunization with tetanus immune globulins (TIG); and (ii) active immunization with vaccine (Tdap or Td). The TIG affords temporary immunity by directly providing antitoxin. This ensures the achievement of protective levels of antitoxin even if an immune response has not yet occurred [1]. The type of treatment depends on the tetanus risk assessment of wounds and the patient's immunization history (Tab. I).

#### *Rationale for DTaP booster*

The immunological pressure exerted by high VC against pertussis achieved in the pediatric age and the relatively short duration of induced immunity against the disease, have allowed a reduction not only in the pertussis incidence in children, but also the chances of natural boosting and the subsequent increasing number of cases among adolescents or adults who have lost their immunological protection and in infants that have not yet begun or completed their primary immunization course [28-31].
For these reasons, most countries that have included vaccination against pertussis in their national immunization schedule, recommend a booster dose at preschool age and a second booster in adolescents, after the primary

**Tab. I.** Preventive strategies of postexposure tetanus.

| Immunization history (number of doses) for tetanus | Tetanus risk assessment of wounds | | | |
|---|---|---|---|---|
| | Low-risk wounds | | High-risk wound | |
| | dT-DTP-dTp[1] | TIG[2] | dT-DTP-dTp[1] | TIG[2] |
| Unknown or < 3 doses | Yes | No | Yes | Yes |
| ≥ 3 doses | No[3] | No | No[4] | No |

[1] Administration of combined vaccine against diphtheria and tetanus (dT) or against diphtheria, tetanus and pertussis (DTP or dTp); [2] administration of anti-tetanus immunoglobulin; [3] yes, if ≥ 10 years have elapsed since the last tetanus toxoid-containing vaccine dose; [4] yes, if ≥ 5 years have elapsed since the last tetanus toxoid-containing vaccine dose.

course of DTaP in the first year of life. Furthermore, in some countries a decennial booster in adults is recommended, in consideration of the relative limited duration of immunity induced both by natural infection and vaccination [32, 33].
In Italy in accordance to the "Lifetime Vaccination Calendar" proposed by a coalition of scientific societies and professional organizations, such as the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI), the Italian Federation of Paediatricians (FIMP), the Italian Society of Pediatrics (SIP) and the Italian Society of General Practitioners (SIMMG), a decennial dTap booster is recommended in adults (e.g., childcare workers, healthcare workers, teachers, etc.) [34].
Furthermore, the current Italian National Immunization Prevention Plan 2012-2014 recommends that the adults who have never been vaccinated for DT receive one dose of dTap among the three doses of the primary course [16].

*Prevention of pertussis in infants (the "Cocoon" strategy)*

Available epidemiological data show that the burden of pertussis in terms of incidence mainly involves infants, adolescents and adults. Infants suffer from the most serious complications of the disease, including death. A decreased risk of infection in newborns can be achieved with the immunization of parents, family members and cohabitants who have a close contact with newborns, who are unvaccinated or incompletely immunized. The booster dose should be administered preferably in the months preceding the birth or immediately after the delivery. The vaccination of pregnant women during the third trimester or late second trimester is recommended also by the ACIP, in conjunction with the American College of Obstetrics and Gynecology and is included in the vaccination schedules of some Western countries, e.g. Netherlands and United Kingdom [32, 33, 35, 36].
This strategy might be combined with a booster targeting adults at high risk of transmitting *B. pertussis* infection to vulnerable infants (e.g., childcare workers, healthcare workers, teachers, etc.), as recommended in the current Italian National Immunization Prevention Plan 2012-2014 [16].

*Objectives of vaccine strategies against diphtheria-tetanus-pertussis implemented in Italy*

The implemented strategies should achieve the following objectives [16]:

- achievement and maintaining VC with three doses of DTaP administered at 24 months of age and with the booster dose at the pre-school age ≥ 95%;
- achievement and maintaining of VC with the "booster" dose of DTaP administered in adolescents ≥ 90%.

## Conclusions

The question "are dT boosters really necessary every 10 years?" should be rephrased as follows: "are dTaP boosters really necessary every 10 years?"

The answer is "yes, certainly", especially taking into account the estimated duration of immunity against pertussis (no more than 10 years) and the need to maintain high protective vaccine-induced antibody titers. Furthermore, the decennial booster involves the advantage of maintaining high protection even against tetanus and diphtheria, thanks to the availability of safe and effective combined vaccines.
It is desirable that this recommendation will also introduced in the future National Immunization Prevention Plan.

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■ Correspondence: Giorgio Zoppi, Department of Prevention, OU Hygiene and Public Health, LHU 4 “Chiavarese”, corso Dante 163, 16043 Chiavari, Genova, Italy - Tel. +39 0185 329041 - E-mail: gzoppi@asl4.liguria.it

# CONTENTS

## Vaccines and vaccination. Improving today and preparing for tomorrow

*Genoa (Italy), 12 September 2014*

**Editorials**



**Reviews**