Eurosurveillance
Europe's journal on infectious disease epidemiology, prevention and control

Vol. 17 | Weekly issue 24 | 14 June 2012

Surveillance and outbreak reports

Research articles

News

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Adverse events following vaccination in the French armed forces: An overview of surveillance conducted from 2002 to 2010

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Citation style for this article:
Mayet A, Haus-Cheymol R, Bouaiti EA, Decam C, Simon F, Mérens A, Spiegel A, Meynard JB, Deparis X, Migliani R. Adverse events following vaccination in the French armed forces: An overview of surveillance conducted from 2002 to 2010. Euro Surveill. 2012;17(24):pii=20193. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20193

Article submitted on 13 December 2011 / published on 14 June 2012

French military personnel are subject to a compulsory vaccination schedule. The aim of this study was to describe vaccine adverse events (VAE) reported from 2002 to 2010 in armed forces. VAE are routinely surveyed by the military Centre for epidemiology and public health. For each case, military practitioners fill a notification form, providing patient characteristics, clinical information and vaccines administered. For this study, VAE following influenza A(H1N1)pdm09 vaccination were excluded. Among the 473 cases retained, 442 (93%) corresponded to non-severe VAE, including local, regional and systemic events, while 31 corresponded to severe VAE, with two leading to significant disability. The global VAE reporting rate (RR) was 14.0 per 100,000 injections. While stationary from 2002 to 2008, the RR increased from 2009. The most important observations were a marked increase of VAE attributed to Bacillus Calmette–Guérin (BCG) vaccine from 2005 to 2008, a high RR observed with the inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine combined with acellular pertussis vaccine (dTap-IPV) from 2008 and an increase in RR for seasonal influenza vaccine VAE in 2009. Our RR for severe VAE (1.1 VAE per 100,000) appears comparable with rates observed among United States civilians and military personnel. The increase observed from 2009 could be partly explained by the influenza A(H1N1)pdm09 pandemic which increased practitioner awareness towards VAE. In conclusion, the tolerance of the vaccines used in French armed forces appears acceptable.

Introduction

Due to their collective lifestyle and their operational imperatives, military personnel are exposed to infections that they can contract during training or overseas missions and that can be prevented by vaccination [1-4]. Thus, according to a vaccination strategy that targets individual and collective protection, French military personnel are subject to a compulsory vaccination schedule at enlistment and during their whole service period (Figure 1). This schedule implies the administration of vaccines that are often injected simultaneously: Bacillus Calmette–Guérin vaccine (BCG), inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine (dT-IPV), which can be also combined with acellular pertussis vaccine (dTap-IPV), inactivated influenza vaccine, $ACYW_{135}$ polysaccharide meningococcal vaccine, subunit hepatitis B vaccine, whole virus inactivated hepatitis A vaccine, typhoid vaccine, live yellow fever vaccine and measles-mumps-rubella vaccine (MMR). Most of these vaccines are administered during the two-month period following enrollment, taking into account previously administered vaccines. Certain specific vaccinations are individualised according to occupational imperatives (e.g. rabies, leptospirosis, tick-borne encephalitis). The vaccination schedule is reconsidered each year and updated according to main epidemiological events.

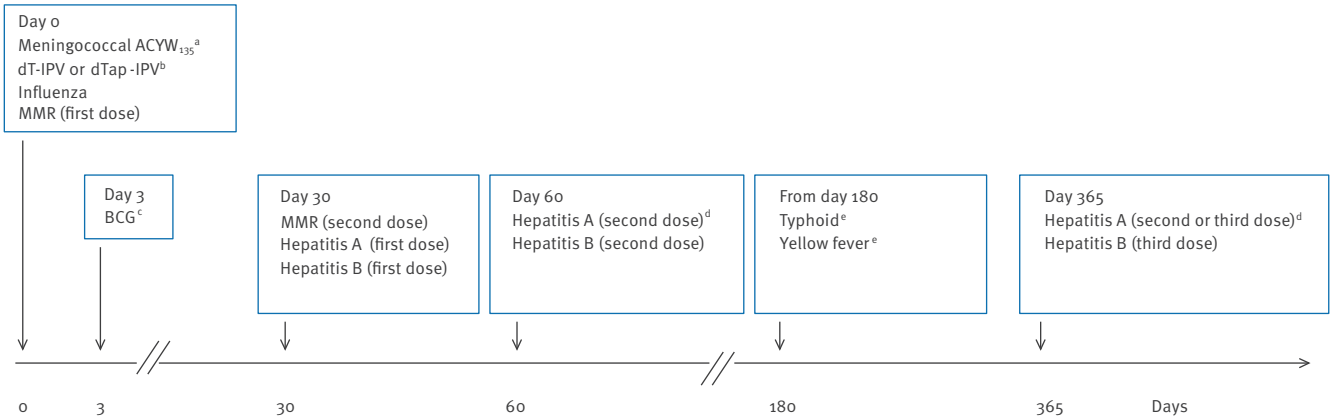
The French military health department that implements this vaccination schedule is also responsible for the vaccine adverse event (VAE) surveillance network in the French armed forces. The objectives of this network are to detect previously unrecognised reactions to current vaccines as well as unusual increases in reported VAE [5]. This article presents the results of VAE surveillance in the French armed forces from 2002 to 2010.

Methods

VAE in the armed forces have been under surveillance since 2002 by the Centre for epidemiology and public health (Centre d'épidémiologie et de santé publique des armées or CESPA) of the French military health department. The military epidemiological surveillance is mandatory and concerns all active military personnel (average of 342,337 personnel-years between

Figure 1

Compulsory vaccination schedule at enlistment for French military personnel likely to be deployed after six month of service, France, 2012



BCG: Bacillus Calmette–Guérin vaccine; dTap-IPV: inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine combined with acellular pertussis vaccine; dT-IPV: inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine; MMR: measles-mumps-rubella vaccine.

A shorter schedule also exists for personnel deployed before six month of service. At enlistment, the vaccination schedules take into account previously administered vaccines.

[a] Between 2002 and 2005, meningococcal AC was also used.

[b] For subjects who did not receive the dTap-IPV booster dose recommended at age 11–13. This vaccine was used starting from 2008. Prior to 2008, only dT-IPV was used.

[c] For healthcare workers only.

[d] For monovalent hepatitis A vaccine two doses, at days 30 and 365; for combined hepatitis A vaccine three doses, at days 30, 60 and 365.

[e] These vaccines have to be injected at least one month before any international deployment.

2002 and 2010, with 35,000 personnel enrolled each year). Every week, military physicians are required to complete a form which mentions the number of cases observed for some monitored health events, including VAE. For each suspected VAE case, the practitioner who sees the patient completes another form providing information concerning the patient, the clinical symptoms and the vaccines administered. The forms are transmitted weekly to the CESPA which analyses the data after checking. Practitioners who sent an incomplete form are re-contacted by the CESPA for data completion. All VAE report forms are then routinely sent to the French Health Products Safety Agency. Cases are classified on the basis of clinical description derived from French drug vigilance guidelines [6]. Two types of VAE are considered:

- Non-severe adverse events: VAE following vaccination, which can be: (i) local (e.g. pain, lump at the injection point, redness >5 cm or other local events like pruritus or haematoma) that persist at least 48 hours; (ii) regional (e.g. ulcer, lymph node tenderness and/or enlargement, adenitis, abscess at the injection site); (iii) systemic (fever ≥38°C or any event thought to be related to vaccination, with sick leave for more than two days);
- Severe adverse events: VAE with hospitalisation, persistent or significant disability, life-threatening illness or death. This category has to be reported immediately to the CESPA and requires a review of medical charts.

Whether severe or non-severe, VAE that are not listed in the French Summary of Product Characteristics (SPC) are also considered as unexpected VAE.

For this study, systemic events that did not lead to a sick leave of more than two days and local events that persisted less than 48 hours were excluded from analyses. VAE following vaccinations with the monovalent A(H1N1)pdm09 vaccine, reported between 2009 and 2010, were also excluded. This is because the influenza A(H1N1)pdm09 vaccination campaign constituted an exceptional phenomenon, which was difficult to compare with what is usually observed in terms of VAE. This data has been previously published [5].

In case of simultaneous administration of several vaccines, the following vaccine suspicion algorithm was used: (i) for local or regional VAE, the vaccine suspected was the vaccine administered at the site of VAE occurrence; (ii) for systemic or severe VAE, all vaccines administered were suspected.

The use of this algorithm explains that the number of suspected vaccines exceeded the number of VAE. Moreover, a vaccination could be responsible of several simultaneous VAE in a same subject (for example, fever associated with a lump at the injection point). For this reason, the number of VAE presented exceeds the number of cases initially reported.

The analysis concerned the 2002–2010 period. The reporting rates for VAE cases were calculated by dividing the number of VAE by the number of military personnel monitored (rates per 100,000 person-years). The vaccine-specific VAE reporting rates (rates per 100,000 vaccinations) were calculated by dividing the number of VAE following a specific vaccine (according to the vaccine suspicion algorithm), by the number of doses distributed according to the French military drug supply department for the same specific vaccine. Reporting rates were compared using negative binomial regressions (model controlled on year for vaccine-specific rates and multivariate model controlled on year, sex and age for VAE cases). Data analysis was performed using Stata version 9.

Results

Vaccine-specific reporting rate for vaccine adverse events

From 2002 to 2010, 798 cases of VAE were reported, of which 170 (21%) were excluded because they did not meet case report criteria. After also excluding the 155 VAE following A(H1N1)pdm09 vaccination, the analyses were performed on 473 VAE cases who presented 634 VAE. After applying the vaccine suspicion algorithm, 681 vaccine injections could be suspected in the occurrence of these VAE and were used for the vaccine-specific reporting rate calculations.

The global VAE reporting rate for the 2002–2010 period was 13.6 VAE per 100,000 injections (681/4,991,270). While the VAE reporting rates did not vary from 2002 to 2008 (reporting rates ranging from 7.9 to 13.7 per 100,000 injections), a significant increase was observed in 2009 and 2010 (respectively 20.7 and 24.9 per 100,000, p<0.001). As shown in Table 1, the dTap-IPV vaccine, used in the French armed forces only since 2008, had the highest global VAE reporting rate of all vaccines considered for the 2002–2010 period (107.2 per 100,000). Among VAE following BCG vaccination (second highest global rate for the 2002–2010 period: 62.8 per 100,000), the multipuncture vaccine (Monovax), used from 2002 to 2005 in armed forces, accounted for a 46.0 per 100,000 reporting rate while the intradermal vaccine (BCG SSI), used from 2006 to 2010, accounted for a 564.0 per 100,000 reporting rate. The dTap-IPV vaccine had the highest reporting rates for local reactions (45.6 per 100,000), systemic reactions (49.6 per 100,000) and severe VAE (2.7 per 100,000). The BCG vaccine had the highest reporting rate for regional reactions (34.8 per 100,000).

No VAE following MMR vaccination, which was used from 2008 in the French armed forces, was reported despite increasing use on account of the recent measles epidemic (9,471 doses injected in 2010) [2].

In terms of evolution of VAE across the period, the most important observations (Figure 2) were: (i) the very high rates in VAE following BCG vaccination from

Table 1

Vaccine-specific reporting rates for vaccine adverse events per 100,000 vaccinations reported in French armed forces according to vaccine suspicion algorithm, France, 2002–2010

Vaccines	Total VAE		Local VAE		Regional VAE		Systemic VAE		Severe VAE		Unexpected VAE	
	N	Rate[a]	N	Rate[a]	N	Rate[a]	N	Rate[a]	N	Rate[a]	N	Rate[a]
BCG (Monovax, SSI)[b]	65	62.8	26	25.1	36	34.8	1	1.0	2	1.9	0	0.0
dTap-IPV (Repevax)	80	107.2	34	45.6	7	9.4	37	49.6	2	2.7	2	2.7
dT-IPV (Revaxis)	75	16.7	36	8.0	6	1.3	27	6.0	6	1.3	0	0.0
Hepatitis A and B (Twinrix)	26	11.2	9	3.9	2	0.9	14	6.1	1	0.4	1	0.4
Hepatitis A (Havrix 1440)	31	6.0	3	0.6	2	0.4	20	3.9	6	1.2	0	0.0
Hepatitis B (Engerix B)	15	9.0	4	2.4	2	1.2	8	4.8	1	0.6	1	0.6
Influenza (Influvac, Mutagrip, Vaxigrip)	159	13.2	50	4.1	19	1.6	79	6.6	11	0.9	2	0.2
Meningococcal AC (Pasteur)[c]	39	12.0	15	4.6	10	3.1	10	3.1	4	1.2	1	0.3
Meningococcal $ACYW_{135}$ (Menomune, Mencevax)	77	11.0	28	4.0	8	1.1	31	4.4	10	1.4	3	0.4
Typhoid (Typhim Vi, Typhérix)	43	5.6	4	0.5	0	0.0	34	4.4	5	0.6	2	0.3
Yellow fever (Stamaril)	71	15.8	6	1.3	16	3.6	43	9.6	6	1.3	0	0.0
Total	**681**	**13.6**	**215**	**4.3**	**108**	**2.2**	**304**	**6.1**	**54**	**1.1**	**12**	**0.2**

BCG: Bacillus Calmette–Guérin vaccine; dTap-IPV: inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine combined with acellular pertussis vaccine; dT-IPV: inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine; VAE: vaccine adverse event.

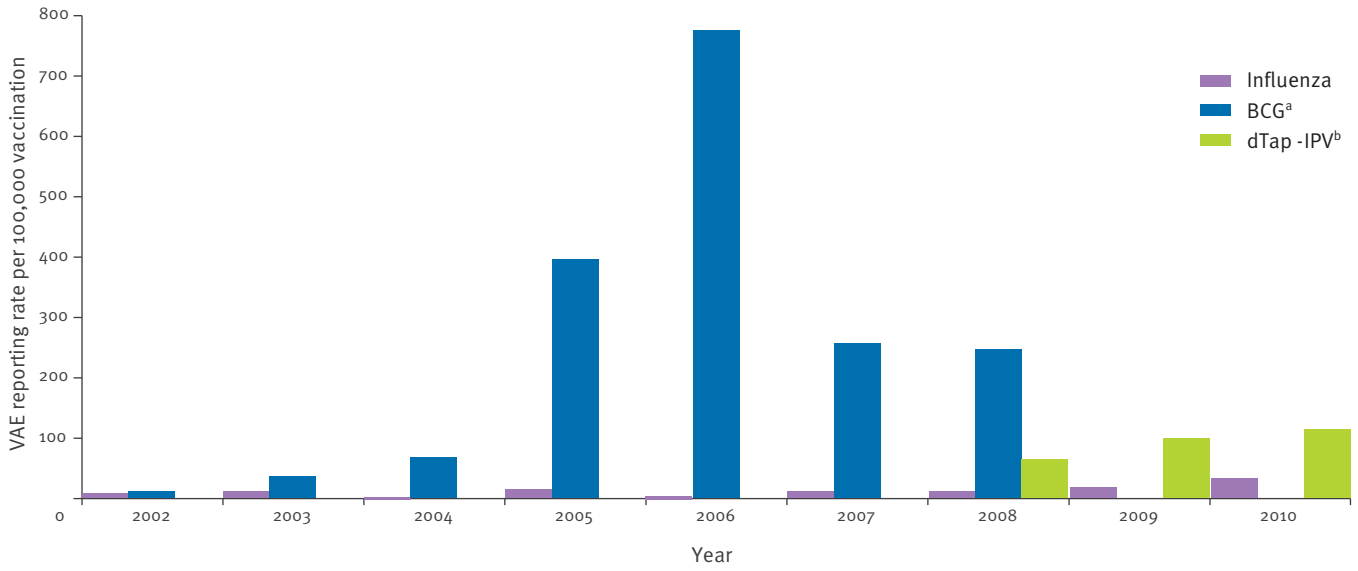
[a] The rate is given per 100,000 vaccinations.

[b] Monovax was replaced by SSI from 2006.

[c] Meningococceal AC vaccine was only used from 2002 to 2004.

Figure 2

Evolution of respective vaccine adverse events rates reported in French armed forces for seasonal influenza, Bacillus Calmette–Guérin and dTap-IPV vaccines, France, 2002–2010



BCG: Bacillus Calmette–Guérin; dTap-IPV: inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine combined with acellular pertussis vaccine; VAE: vaccine adverse events.

[a] BCG multipuncture vaccine (Monovax) was replaced by BCG intradermal vaccine (SSI) in 2006.

[b] dTap-IPV was used starting 2008.

2005 to 2008 (p<0.001), the reporting rate reaching 785.2 VAE per 100,000 vaccinations in 2006; (ii) the high reporting rates observed with the dTap-IPV vaccine from the beginning of its use, with a tendency to increase between 2008, 2009 and 2010 (respectively 65.5, 100.3 and 115.7 VAE per 100,000 vaccinations; p=0.2); (iii) an increase in seasonal influenza vaccine VAE reporting rates from 2009 (17.9 VAE per 100,000 in 2009 and 32.8 VAE per 100,000 vaccinations in 2010; p=0.05).

Characteristics of vaccine adverse events cases

Among the 473 military personnel who presented a VAE, 142 (30%) were women and 213 (45%) belonged to the Army. The median age of cases was 26 years (interquartile range (IQR) [21-33]). Multivariate analysis showed a 1.9 times greater risk of VAE among women (33.5 versus 12.5 cases per 100,000 persons-years among men; p<0.001). In addition, being under 20 yielded a 15.7 times greater risk of VAE than being 50 and older (94.6 versus 5.5 cases per 100,000 persons-years; p<0.001).

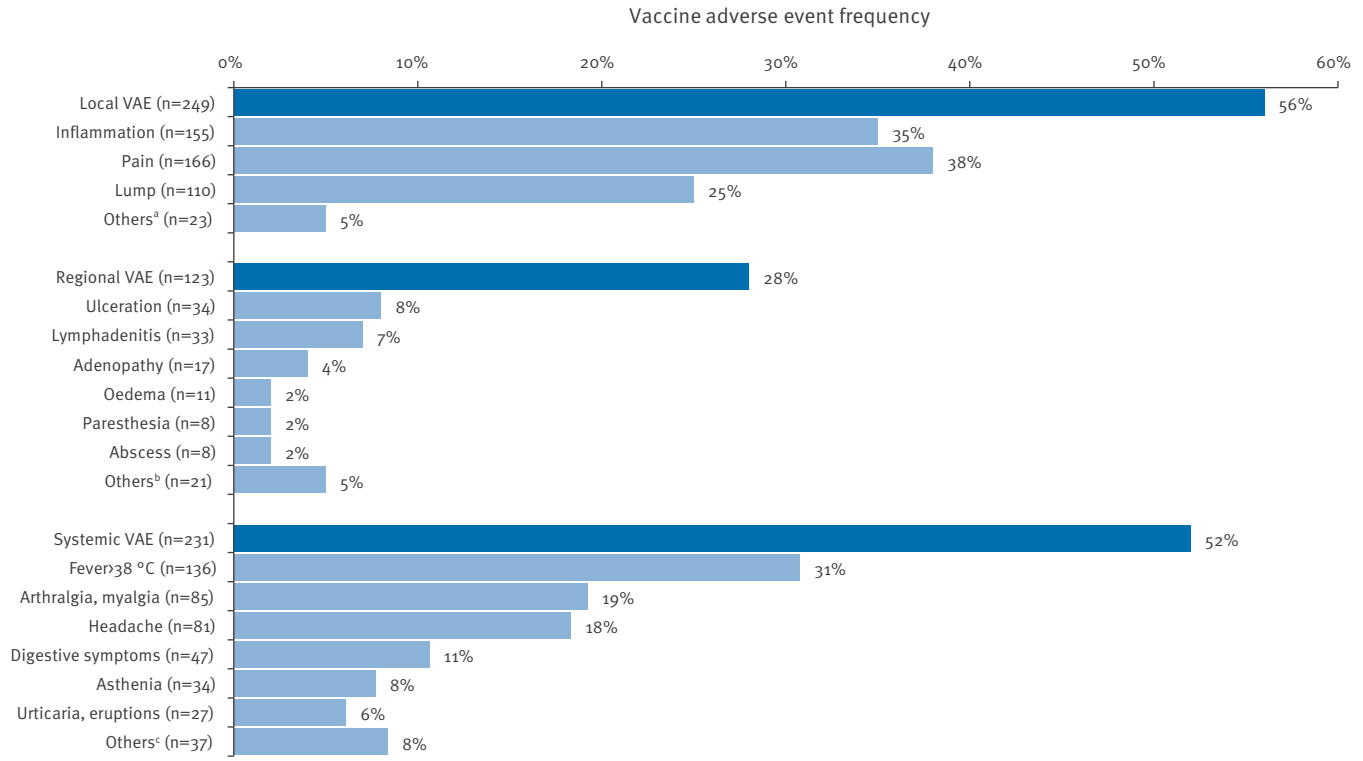
Severity of the vaccine adverse events

Among the 473 cases reported, 93% were non-severe. These 442 cases corresponded to 603 VAE, given the associations observed in 150 cases (34%) of several types of VAE. Two hundred and forty-nine cases presented a local VAE (56%), 123 (28%) presented a regional VAE and 231 (52%) presented a systemic VAE (Figure 3). Local VAE were mainly characterised by pain (38%), redness (35%) and lump at the injection point (25%). Clinical features of systemic VAE frequently included an influenza-like syndrome most often with fever, arthralgia and headaches. The mean time lapse from vaccination to the occurrence of the VAE was 2.6 days for local VAE (median: 0.7, IQR: 0.2–1.2 days), 8.4 days for regional VAE (median: 1.1, IQR: 0.4–6.0 days) and 1.6 days for systemic VAE (median: 0.8, IQR: 0.3–1.9 days).

Only 31 VAE (7%), corresponding to the same number of cases, were considered as severe because they led to hospitalisation (Table 2). The mean time lapse from vaccination to the occurrence of the severe VAE was 26.2 days (median: 2.0, IQR: 1.0–6.0 days). The maximal time-lapse (563.0 days) was observed for a macrophagic myofasciitis following hepatitis A vaccination. Neurological syndromes were predominantly severe headaches (7 cases) which sometimes occurred in a context of meningeal-like syndrome (3 cases). One subject developed acute leucoencephalomyelitis three weeks after seasonal influenza vaccination, leading to cognitive and sensory sequelae. Still's disease, a rheumatic disorder, occurred in a case aged 20 who had received yellow fever and hepatitis A vaccines the same day. A few hours after vaccination, the patient presented transitory dysesthesia in the median nerve area of the limb where the yellow fever vaccine had been injected. Two months later, this case presented a polyarthritis which led to significant lack of mobility. The BCG vaccine was responsible for two severe

Figure 3

Frequency of vaccine adverse events (n=603) reported by French military personnel (n=442), France, 2002–2010



VAE: vaccine adverse event.

[a] Refers to other types of local vaccine adverse events.

[b] Refers to other types of regional vaccine adverse events.

[c] Refers to other types of systemic vaccine adverse events.

local ulcerations, probably aggravated by poor hygiene during a training period occurring after vaccination. The three cases of urticaria reported as severe VAE were not life-threatening but were treated and monitored in hospital, unlike the urticaria cases reported as non-severe VAE which were treated in the medical department of the military unit. This situation was also observed for headaches and influenza-like syndromes that were reported as severe VAE. Finally, although the outcome of the macrophagic myofasciitis is unknown, all other reported severe VAE, with the exception of the cases of leucoencephalomyelitis and Still's disease, regressed without sequelae.

Only nine unexpected VAE were reported (2%), including ear, nose and throat disorders (ENT) symptoms (epistaxis, hypoacusis tinnitus), ophthalmological symptoms (temporary loss of visual acuteness, central chorioretinitis), one case of myopericarditis (which was also considered as a severe VAE), one of psoriasis, and one of monoplegia of the vaccinated limb.

Discussion

Reporting the vaccine adverse events

The strength of this study is that it provides recent data concerning VAE for a nine-year period in a healthy, high-vaccinated and adult (18–65 age stratum) population. As most of the vaccinations administered in armed forces are compulsory and military personnel can consult a physician in the medical department that performed the vaccine injection, it is likely that our data could be representative of the majority of VAE that occurred in this population. The high exclusion rate observed over the study period (21%) accounts to the reliability of our data: if so many patients consulted for minor symptoms, there is likely that the surveillance system would not miss real VAE cases. However, the use of a passive reporting system may expose to under-reporting from some practitioners.

Given the absence of reliable data concerning doses injected, the number of doses distributed was chosen as denominator for vaccine-specific rate calculations,

Table 2

Clinical features and administered vaccines for cases of severe vaccine adverse events (n=31) reported in French armed forces, France, 2002–2010

Type of VAE	Symptoms (number of cases)	Sick leave length in days	Time-lapse from injection to VAE in days	Vaccines administered[a]
Local VAE	Ulceration (n=1)	16	73	BCG
	Abscess (n=1)	1	2	BCG
Neurological syndromes	Headache (n=2)	1	2	Meningococcal AC, dT-IPV, typhoid
		2	NN	Meningococcal $ACYW_{135}$, yellow fever, typhoid, influenza
	Meningeal-like syndrome (n=3)	3	3	Meningococcal AC, dT-IPV
		2	2	Yellow fever
		NN	1	Meningococcal $ACYW_{135}$, hepatitis A
	Headache and vertigo (n=2)	2	1	Yellow fever, hepatitis A, typhoid
		1	5	Yellow fever, dT-IPV
	Cerebellar syndrome (n=1)	18	1	Hepatitis A, meningococcal AC
	Obnubilation (n=1)	1	1	dT-IPV
	Leucoencephalomyelitis (n=1)	180	22	Influenza
	Monoplegia of vaccinated limb (n=1)	NN	5	Hepatitis A and B, typhoid
Metabolic syndromes	Thrombopenia/bleeding (n=3)	NN	10	Influenza, hepatitis B
		20	6	Meningococcal $ACYW_{135}$, influenza
		20	6	Meningococcal $ACYW_{135}$, influenza
	Renal insufficiency (n=1)	NN	3	Influenza, yellow fever
	Hypoglycemia (n=1)	NN	2	Influenza
Miscellaneous syndromes	Urticaria (n=3)	1	1	Influenza
		3	0	Hepatitis A
		1	0	Meningococcal $ACYW_{135}$, typhoid
	Macrophagic myofasciitis (n=1)	NN	563	Hepatitis A
	Influenza-like syndrome (n=4)	3	0	dT-IPV, meningococcal AC
		NN	0	Typhoid
		13	6	Meningococcal $ACYW_{135}$, dT-IPV
		4	1	Meningococcal $ACYW_{135}$, dTap-IPV
	Myopericarditis (n=1)	7	2	Influenza
	Vagal malaise (n=2)	1	0	Influenza, meningococcal $ACYW_{135}$, dTap-IPV
		2	1	Influenza
	Still's disease (n=1)	116	60	Yellow fever, hepatitis A
	Spreading myalgia (n=1)	45	6	Hepatitis A, meningococcal $ACYW_{135}$

BCG: Bacillus Calmette–Guérin; dT-IPV: inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine; dTap-IPV: inactivated diphtheria-tetanus (toxoids)-poliovirus vaccine combined with acellular pertussis vaccine; NN: not known; VAE: vaccine adverse event.

[a] In cases of vaccine association, the first vaccine of the list is the one that was initially suspected by the practitioner who performed the vaccination.

which could lead to an underestimation of VAE. However, this number may not be too different from the number of doses really injected if considering that military units, constrained by economic imperatives, order vaccines as and when required, keeping little stock which may expire.

VAE constitute a relatively rare phenomenon in the French armed forces if we consider the large number of vaccinations performed (around 500,000 each year). The reporting rate of 14 VAE per 100,000 injections observed in French armed forces appears higher than the rate (4 VAE per 100,000) observed in United States (US) general population aged 18–65 years for the 1991–2001 period [8]. Although non-severe VAE are not routinely monitored in the French civilian population, a study using the drug vigilance database of a pharmaceutical laboratory showed a reporting rate of 20 VAE per 100,000 for the 2000–2010 period, which could correspond to a 7 per 100,000 reporting rate among 18–65 year-olds if it is assumed that the distribution of VAE according to age is the same in France as in US [9]. The higher reporting rate observed in our study could reflect better reporting of non-severe VAE by military physicians, who could be more inclined to follow instructions to report VAE compared to civilian

physicians, the French military surveillance system being compulsory and the subject of a training course. This hypothesis is also supported by the higher proportion of reported severe VAE in the US civilian data (14% versus 7% among French military forces). Moreover, the severe VAE reporting rate among French armed forces (1.1 per 100,000) was comparable with rates observed among US civilians (0.6 per 100,000) and US military personnel for the 1998–2002 period (0.8 per 100,000 for yellow fever vaccine and 1.3 per 100,000 for typhoid vaccine) [10]. However, these cross-national comparisons in reporting rates are problematic due to differing populations, reporting procedures and exclusion criteria.

The highest reporting rate, when considering the whole period studied, was observed with the dTap-IPV vaccine. As this vaccine has been used only since 2008 in the French armed forces, this high reporting rate could reflect the fact that military physicians perceived dTap-IPV as a "new" vaccine, leading to a tendency to more complete reporting [11]. This more complete reporting, which may not be the consequence of diagnosis biases, could lead to more representative rates even if they are unusually high. The dTap-IPV vaccine is also known to be implicated in certain non-severe VAE. A study conducted among US healthcare personnel in 2006 showed that 68% of vaccinated subjects reported an injection site reaction and 10% reported subjective fever [12]. However, although the higher severe VAE reporting rate also concerned the dTap-IPV vaccine in our data, the VAE reported were relatively benign. A study conducted from 2004 to 2008 concluded that the dTap-IPV vaccine has a similar safety profile to that of dT-IPV vaccine in terms of severe VAE [13].

High reporting rates were observed with the BCG vaccine for the study period, particularly with the intradermal vaccine. In the French general population, ulcerations have been reported to follow 1 to 2% of BCG vaccinations [14]. The peak in reported VAE observed in 2006 coincided with the withdrawal of multipuncture BCG vaccine (Monovax) in France, replaced by the intradermal BCG vaccine (BCG SSI) [15]. Practitioners were not accustomed to the administration of this new vaccine, which could have involved some administration errors and led to the observed increase in VAE this year [16]. This led French health authorities to publish recommendations of good practice [17]. From 2007, BCG vaccination was limited to certain populations at risk and a decrease in number of injected doses occurred from this year in the French armed forces (387 in 2007 versus 1,165 in 2006).

Finally, an increase in reported seasonal influenza VAE occurred at the end of 2009. It mainly involved non-severe events and probably reflects stimulated reporting in the context of the upcoming influenza A(H1N1) pdm09 pandemic [18]. Subsequently, 155 VAE following pandemic influenza vaccination were reported in the French armed forces within a six-month period while VAE incidence for all other vaccines was only 45 cases for the same period, which is mainly explained by an over-reporting effect [5]. It is possible that this episode increased practitioner awareness towards VAE reporting, which could explain the increase in reporting observed in 2009 and 2010 while the VAE reporting rate was stationary between 2002 and 2008. The numerous VAE following dTap-IPV vaccination reported from 2008 may have also contributed to this observed increase.

Taking into account the number of military personnel monitored, the VAE reporting rate was the highest among subjects under 20 years of age (94.6 cases per 100,000 person-years). This age stratum corresponds to the personnel recently enlisted and consequently more likely to receive a number of vaccines due to the military vaccination schedule.

Severity of vaccine adverse events

Most of the VAE reported (93%) were non-severe effects, which, in addition to the relatively low reporting rates observed, amounts to an acceptable tolerance of vaccines among French military personnel. Most of the 31 severe VAE reported between 2002 and 2010 were considered as severe only when hospitalisation of concerned cases occurred. For example, the three urticaria cases were only characterised by a diffuse superficial eruption, without impact on respiratory function or circulation, and regressed rapidly after anti-histaminic treatment. In addition, 27 other subjects presented a cutaneous eruption which fitted the characteristics of diffuse superficial urticaria. These cases were considered as non-severe VAE because they were treated in the medical department of the military unit and monitored for a few hours, without hospitalisation. It is true that the reporting rate for life-threatening anaphylactic reactions following vaccination is very low, ranging from one to three cases per million vaccinations [19]. Thus, the hospitalisation criterion in the definition of severe VAE does not always reflect the clinical severity of the case's status because the decision to hospitalise also depends on other factors: presence of a nearby medical facility, experience of the general practitioner who initially treats the case, or operational imperatives.

On a case by case basis, causal attribution of VAE to vaccines is scientifically difficult [20], particularly for rare or unexpected events, and this difficulty increases in case of simultaneous injection of several vaccines, which concerned 58% of severe VAE observed in our study (18/31). Finally, VAE cases constitute a minor phenomenon if compared to the many cases avoided by vaccination concerning some diseases. Significant decreases in meningococcal meningitis and hepatitis A incidences were thus observed following the implementation of systematic vaccination at enlistment in armed forces [21-23].

Conclusion

VAE appears to be relatively rare in French armed forces, particularly severe VAE. Our results are concordant with previous research and account for an acceptable tolerance of vaccines. The French armed forces, which enrol around 35,000 personnel and perform more than 500,000 vaccinations each year, are an important vaccine vigilance observatory in France while the surveillance of non-severe VAE is not compulsory in civilian population [24]. The monitoring of VAE remains topical in armed forces because it assures military personnel that safety of required vaccines is taken seriously and constitutes an indirect indicator of the acceptability of vaccination campaigns from patient and practitioner viewpoints.

Acknowledgments

Authors would like to thank all the military physicians and the staff of the Epidemiological and public health centre who participated actively in the military epidemiological surveillance network by way of the quality of their notifications and reports.

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Description of measles D4-Hamburg outbreak in Hamburg, Germany, December 2008 to June 2009, which disproportionally affected a local Roma community

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Citation style for this article:
Hegasy G, Kätzner K, Helle M, Mankertz A, Baumgarte S, Wille A, Fell G. Description of measles D4-Hamburg outbreak in Hamburg, Germany, December 2008 to June 2009, which disproportionally affected a local Roma community. Euro Surveill. 2012;17(24):pii=20194. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20194

Article submitted on 27 October 2011 / published on 14 June 2012

From December 2008 to June 2009 a measles outbreak occurred in the Federal State of Hamburg, Germany. The outbreak affected 216 persons and was caused by a new measles strain termed D4-Hamburg which led to consecutive outbreaks between 2009 and 2011 in at least 12 European countries. Here, we describe epidemiological characteristics of the outbreak and evaluate the control measures taken in Hamburg. In one of the seven boroughs of Hamburg a local Roma community comprised more than 50% of the notified cases. We compared in a stratified analysis the age distribution of these cases with cases of fellow citizens who did not belong to the Roma community. The age group of infants (0-11 months) comprised 33% among the non-Roma measles cases, while in the Roma community only 4% belonged to this stratum. In the stratum of 5-17 year-olds only 8% were affected among the non-Roma cases, whereas in the Roma community 50% belonged to this age group. We discuss the influencing factors that might have led to this difference in age distribution between the two groups.

Background

In December 2008 a measles outbreak started in the city of Hamburg, reached its peak during February and March 2009 and ended in June 2009 [1]. As demonstrated later by molecular typing, this outbreak was the origin of European-wide spread of a measles strain closely related to D4-Enfield, but later classified as a separate strain on the basis of sequence analysis. Consequently this strain was named D4 Hamburg. The spread of this D4-Hamburg virus continued in Europe in the following three years and led to consecutive outbreaks in Bulgaria, Poland, Ireland, Northern Ireland, Austria, Greece, Romania, Turkey, Macedonia, Serbia, Switzerland and Belgium with over 25,000 persons infected [2].

The following surveillance data on the D4-Hamburg outbreak concerning age, vaccination status and hospitalisation rate of cases have been published earlier [1,2] and are only briefly summarised here: The age range of cases was 1 day to 54 years; the mean age was 14.6 years and the median age was 13.5 years. A vaccination card was available for 196 of 216 cases (91%). Of these, 157 cases had no record of immunisation with measles-containing vaccine (MCV), including 28 cases below the recommended vaccination age of 11 months. Of 39 cases with a record of MCV immunisation, one dose was documented for 33 cases, two doses for three cases, and for three cases the record was ambiguous. Of the 33 cases with one documented dose, 26 were contacts who had received a combined measles-mumps-rubella vaccine (MMR) as post-exposure prophylaxis, but still developed the disease. No case fulfilled the criteria for application of passive protection using antiserum according to guidelines of the German Standing Committee on Vaccination (Ständige Impfkommission, STIKO) [3]. The hospitalisation rate was 40%, with pneumonia and otitis media as the most frequent complications. No fatality was reported in this outbreak.

Measles virus infection has been a notifiable disease in Germany since 2001 according to the Communicable Disease Law Reform Act (Infektionsschutzgesetz, IfSG). Vaccination guidelines are provided by the STIKO, which is affiliated to the Robert Koch Institute (RKI) representing the federal institution for disease prevention and control in Germany. According to STIKO guidelines, a first dose of MCV should be given at the age of 11 to 14 months and a second dose at the age of 15 to 23 months, preferably using combined MMR vaccine [3]. For individuals missed in the regular schedule, catch-up vaccination is recommended. Since 2010,

the STIKO has additionally recommended a single dose of MCV to be given to any person born after 1970 who has not received two doses of MCV or does not have a medical record of a subsided measles infection [4]. This decision to extend MCV immunisation to adults was taken as a result of continuing measles outbreaks in Germany, including the outbreak described here [5].

To meet the WHO European Region measles elimination target by 2015, a vaccination coverage of 95% for two doses of MCV is necessary [6]. According to assessment at school entry, adequate vaccination status has increased in Germany over the last 10 years, but coverage is still below this threshold (Germany 90.2%, Hamburg 90.5%) [7]. Furthermore, underserved minorities have repeatedly been involved in large outbreaks in Germany [8,9]. Here, we describe the measles outbreak in the Federal State of Hamburg in 2008-09, which disproportionally affected a local Roma community.

Methods

For the D4-Hamburg outbreak description, data from the electronical surveillance system were re-evaluated according to IfSG using SurvNet software of RKI. These notification data include case information on age, sex, onset and duration of disease, clinical symptoms, laboratory confirmation, epidemiological links between cases and vaccination status if available. In addition, semi-structured records on contact tracing and outbreak containment measures of the seven public health departments of Hamburg were evaluated.

Cases were defined as persons with a) a generalised maculopapular rash for more than three days AND fever AND at least one of the following symptoms: cough, coryza, conjunctivitis or Koplik spots, OR b) a generalised maculopapular rash for more than three days AND/OR fever, AND laboratory diagnosis of measles infection. Persons with laboratory diagnosis of a measles vaccine strain were excluded.

Measles virus RNA in nasopharyngeal swabs or oral fluid was detected by real-time RT-PCR performed at the municipal Institute for Hygiene and Environment as described earlier [10]. Genotyping was performed at the National Reference Centre (NRC) for Measles, Mumps, and Rubella as described earlier [11].

Analysis of the cases' areas of residence by postcode and cartography was performed employing the Geographical Information System software ESRI ArcGIS.

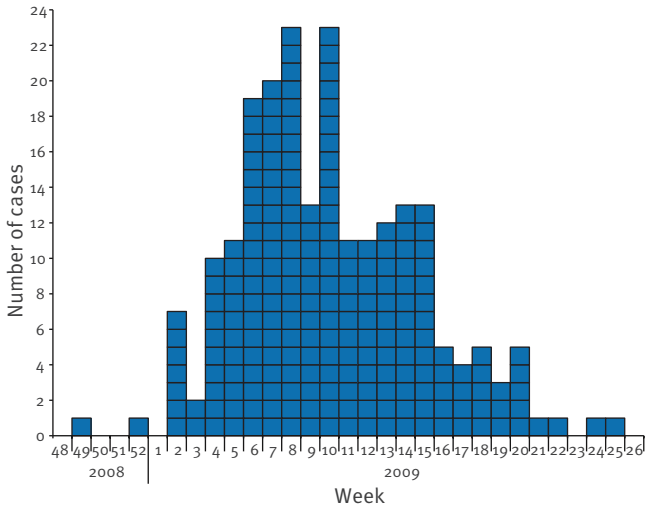
Outbreak description

Epidemic curve and geographical distribution

The outbreak started in 2008 with a case in week 49 and a second case in week 52. It continued in 2009 from week 2 to week 25 with 214 cases (Figure 1). The case in week 52 of 2008 was initially termed as the index case for Hamburg, although the patient falling ill

Figure 1

Epidemic curve of measles D4-Hamburg outbreak, Hamburg, 1 December 2008–17 June 2009 (n=216)



Cases were assigned to the corresponding week according to appearance of first measles symptoms.

Figure 2

Outbreak location in the Federal State of Hamburg, Germany, bordering Lower Saxony and Schleswig-Holstein, 1 December 2008–17 June 2009 (n=216)

in week 49 of 2008 was retrospectively counted in as belonging to the outbreak as well. The outbreak lasted for 29 weeks with highest case numbers between week 6 and week 10 of 2009 (Figure 1).

Between week 3 and week 18 of 2009 the outbreak expanded to Lower Saxony, a bordering federal state south of Hamburg (Figure 2). Here, 53 cases were notified. Within the city limits of Hamburg the outbreak was mainly localised in the boroughs south of the river Elbe with a focus on the boroughs of Hamburg-Mitte and Harburg (Figure 3). To analyse the spatial distribution of the outbreak in more detail, postcodes of the case's place of residence were mapped using geoinformation software at the Centre for Infectious Disease Epidemiology. As demonstrated by this approach, eight of 21 postcode areas were affected in this borough. The highest incidences were restricted to the two postcode areas in the district of Wilhelmsburg (Figure 4).

Clinical and laboratory-confirmed cases

For 207 of the 216 cases the diagnosis was based on the clinical presentation and 190 of the 216 cases were linked to another case epidemiologically. For 149 of the 216 cases a laboratory confirmation was notified representing 69%. For 100 of them laboratory diagnosis was based on PCR, of which 78 were confirmed by PCR alone, 20 by PCR in conjunction with IgM detection, and one each by PCR in combination with rising IgG titre or virus isolation. A further 44 of the 149 laboratory-confirmed diagnoses were based on IgM detection alone, while four cases were based solely on rising IgG titre. One case was confirmed by virus isolation in conjunction with IgM detection.

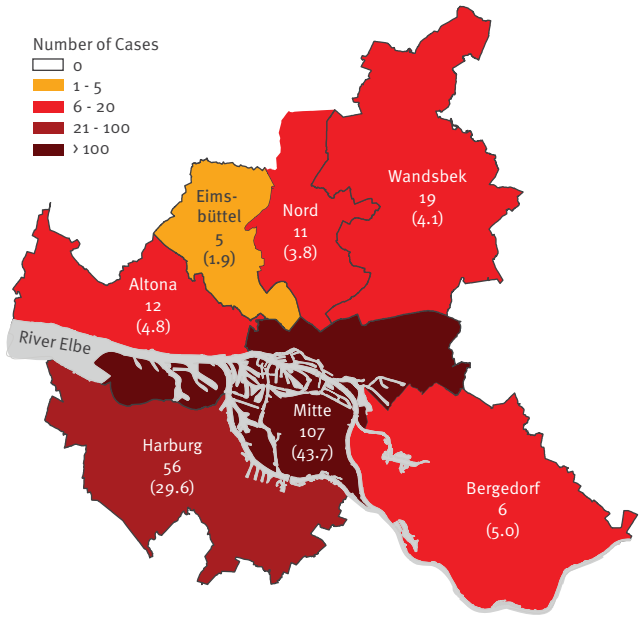
In addition to patients who received laboratory confirmation of measles infection by their family doctor, physicians of the public health departments offered immediate laboratory diagnostics during contact tracing to potentially infected individuals. To this end nasopharyngeal swabs or oral fluid were taken and analysed for measles virus RNA by real-time RT PCR. Laboratory analyses were offered free of charge to the public health departments of Hamburg by the municipal Institute for Hygiene and Environment. Of 174 persons from whom nasopharyngeal swabs or oral fluid were taken during contact tracing, 100 were found positive. This represents 67% of all laboratory-confirmed cases of the outbreak. For sequencing and genetic strain analysis, 23 swabs were sent to the NRC. Twelve of them were identified as the virus strain later termed D4-Hamburg [2]. Ten samples that were found positive in diagnostic PCR could not be sequenced successfully. For one sample sequencing revealed an infection with the vaccine virus, and consequently this patient was not counted as a case.

Index case

On 27 and 28 December 2008, a patient in their 20s presented to the outpatient department (OPD) of a hospital in Hamburg. The patient had suffered from a sore throat since 24 December 2008 and had developed a rash after taking acetylsalicylic acid. Under the assumption of streptococcal pharyngitis and drug eruption ambulatory treatment with amoxicillin, paracetamol and an anti-histamine was given. Because the patient's condition deteriorated, they presented on 29 December 2008 to the OPD of a second hospital where infection with measles virus was suspected and the patient was hospitalised. As any case of

Figure 3

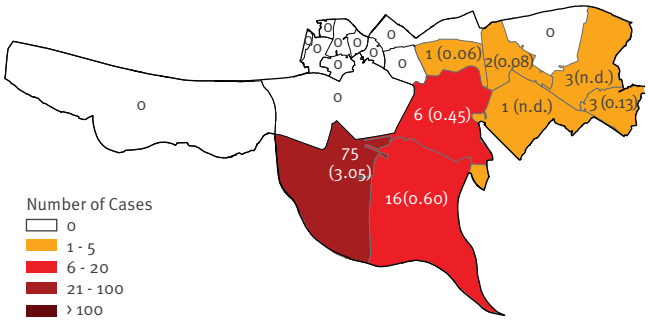
Measles cases in the seven boroughs of Hamburg, 1 December 2008–17 June 2009 (n=216)



Incidence per 100,000 is given in parentheses.

Figure 4

Measles cases in the borough of Hamburg-Mitte by postcode areas of residence, 1 December 2008–25 May 2009 (n=107)



Incidence per 100,000 is given in parentheses. For two postcode areas extending outside the borough borders of Hamburg-Mitte, the incidence was not determined (n.d.).

clinically suspected measles has to be notified according to the IfSG, the responsible public health department received a report on this case on 31 December 2008. Laboratory diagnosis later confirmed the infection by demonstrating positive IgM titre against measles virus and increasing IgG titres.

First and following generations of cases

The OPD visited first by the index patient was highly frequented between Christmas and New Year. The waiting area was overcrowded and patients had to wait for several hours. Potentially infectious patients were not separated. Between 8 and 11 January 2009, five persons that had been present in this OPD on 27 or 28 December 2008 fell ill with measles. These comprised two patients present in the waiting area for accident and emergency consultation, four persons accompanying patients to the OPD for medical advice in internal medicine or accident and emergency, and one hospital staff. All five cases were notified by their physicians according to the IfSG. Further spread from these five cases to household contacts was traced by the public health departments. In the entire outbreak, one or more, transmission chains were identified at each of the affected publicly accessible sites such as kindergartens, primary and secondary schools, shopping centres, and waiting areas of medical practices. Exact numbers cannot be given because not all records on transmission sites were accessible for retrospective evaluation.

Spread in a Roma community

On 26 January 2009, the public health department of Hamburg-Mitte received a report on a measles case in a woman in her 20s who was in her 16th week of pregnancy when she was diagnosed with measles on 16 January 2009. As part of the contact tracing activities, a home visit was paid to this patient. She declared unquestioned that she belonged to a settled Roma community that traditionally lives in this borough of Hamburg. She further stated that all contact persons named by her also belonged to that community. Consequently, she was regarded as the index case for the Roma community. In the following nine weeks, 60 persons who indicated that they belonged to the same community fell ill with measles. Of those, 56 cases lived in Hamburg-Mitte which represents 52% of the 107 cases reported in this borough. The last case of the community fell ill on 19 March 2009. Additionally, in Lower Saxony seven cases stated that they belonged to the ethnic group of Roma.

On subsequent home visits paid to the community, two more cases were identified who had occurred earlier than the case regarded initially as the Roma community index: On 2 December 2008, an adolescent from the community was diagnosed with measles. The patient had been visited by relatives from London in the month of November 2008. This case was notified, but notification reached the responsible public health department with a delay of several weeks. Although no link could be found to the patient who later presented to the OPD, this adolescent was most likely the true index case of the measles D4-Hamburg outbreak. On 17 December 2008 the patient's older sibling fell ill with measles. No notification of this case was received although the patient had been seen by a physician. The older sibling was acquainted with the pregnant woman formerly regarded as the Roma community index case, but stated no personal contact to her. Even assuming a maximal length of infectious and incubation period (9 and 21 days, respectively), disease onset in the older sibling occurred at least five days too early to allow a direct virus transmission from them to the pregnant woman. Thus, it is highly probable that at least one more connecting case occurred in the community that was not seen by a physician, misdiagnosed or not notified.

Control measures

In all boroughs of Hamburg control measures were taken, but actions were focused on those boroughs south of the river Elbe where most cases were reported. Visits were paid to 34 community facilities such as kindergartens, primary schools and secondary schools. A community facility was selected for a visit if a case had occurred there, if a contact of a case attended that facility, or if it was located in a district highly affected by the outbreak. On these occasions, 364 doses of MCV were given on site to children as well as teachers and staff. Another 497 children who could not produce parental consent to vaccination were advised to receive MCV from their family doctor. A total of 701 persons attending or working at the community facilities could not provide proof of MCV immunisation or a medical record of a subsided measles infection, and were, based on IfSG, suspended for two weeks from their last potential contact to an infectious person.

In the context of enhanced measles surveillance, the frequency of case notifications from local health departments to RKI was increased from weekly to daily. In parallel, surveillance data were evaluated and compiled by the Centre for Infectious Disease Epidemiology for briefings of the State Health Department of Hamburg and for press releases targeting either the general public or specifically local physicians.

To provide information on measles to residents of affected districts and to offer low-threshold access to vaccination, a promotional bus was borrowed from the German Organisation for the Protection of Children (Deutscher Kinderschutzbund Hamburg, DKSB) and allocated for medical advice on measles prevention. Staff included two physicians, two assistants, and at least two interpreters. Interpreters were health mediators of the programme With Migrants for Migrants (Mit Migranten für Migranten, MiMi) which is described in detail elsewhere [12]. The promotional bus was opened on six occasions for four hours at central public places in the borough of Hamburg-Mitte. On these occasions

964 consultations were requested and 18 MMR vaccinations were given.

To specifically reach the Roma community, 10 home visits were paid by the Public Health Department of Hamburg-Mitte to Roma patients and their contacts between 19 January and 5 February 2009. Staff included a physician and at least one assistant. On these occasions, vaccination cards were controlled and MMR immunisation was offered as well as laboratory diagnostics by nasopharyngeal swabs or oral fluid. No data were recorded separately for the Roma community concerning the number of persons seen, contact persons traced or vaccinations given, but on these occasions 19 PCR-positive measles cases were identified in the community.

Age distribution of cases in Hamburg-Mitte

Of 107 cases notified in the borough of Hamburg-Mitte, 56 belonged to the Roma community. We considered these surveillance data as suitable for further analysis with respect to the affected Roma and non-Roma community in Hamburg-Mitte. No significant difference in sex distribution of infected individuals was seen between both groups (non-Roma: 28 male and 23 female, Roma: 29 male and 27 female, chi-squared test, two-tailed p value: 0.747). As shown in Figure 5A the mean age of the cases was 10.1 years for the Roma group and 11.8 years for the non Roma group, while their median age was one year for the non-Roma and nine years for the Roma group. As the difference between mean and median in the non-Roma group pointed to a non-Gaussian distribution, we wanted to study the age distribution in both groups in more detail and therefore defined five age groups for a stratified analysis. Stratification was chosen as follows according to the standard vaccination schedule as recommended by STIKO guidelines [3]: (i) infants under the age for receiving MCV (≤11 months), (ii) age range for scheduled administration of two doses of MCV (12–23 months), (iii) age range without scheduled vaccinations (2–4 years), (iv) age range for further scheduled and catch-up vaccinations (5–17 years), (v) adults (≥18 years). As shown in Figure 5B, the age distribution in the strata (i) and (iv) differed between the groups.

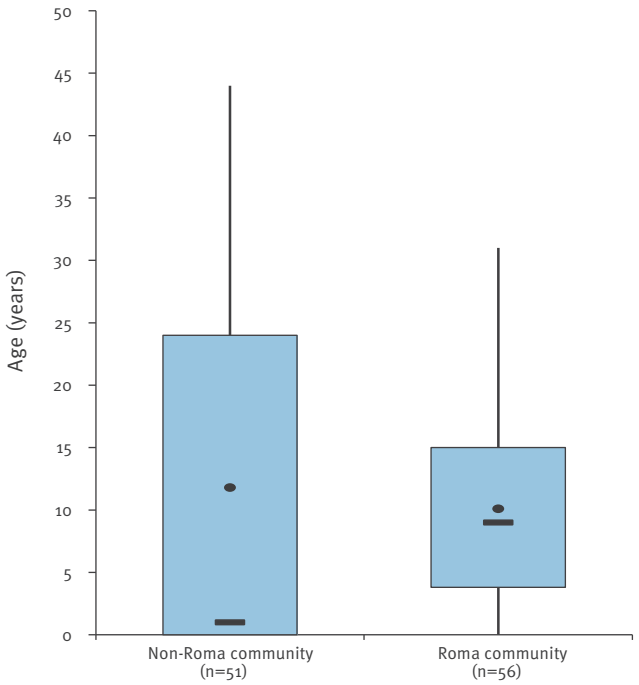
Discussion

For outbreak surveillance to be sufficient, 80% of clinically diagnosed measles cases should according to the World Health Organization's guidelines, be laboratory-confirmed [6]. In the outbreak described here, 149 of 216 cases (69%) were confirmed by laboratory analyses. Of these 100 were identified by PCR from nasopharyngeal swabs or oral fluid, representing 67% of the tests. These PCR diagnostics were offered during contact tracing and home visits by the public health departments and performed at the municipal Institute for Hygiene and Environment. In contrast to serological analyses as a standard tool for laboratory diagnosis of measles infection, taking of nasopharyngeal swabs or oral fluid for PCR is non-invasive and was easily

Figure 5

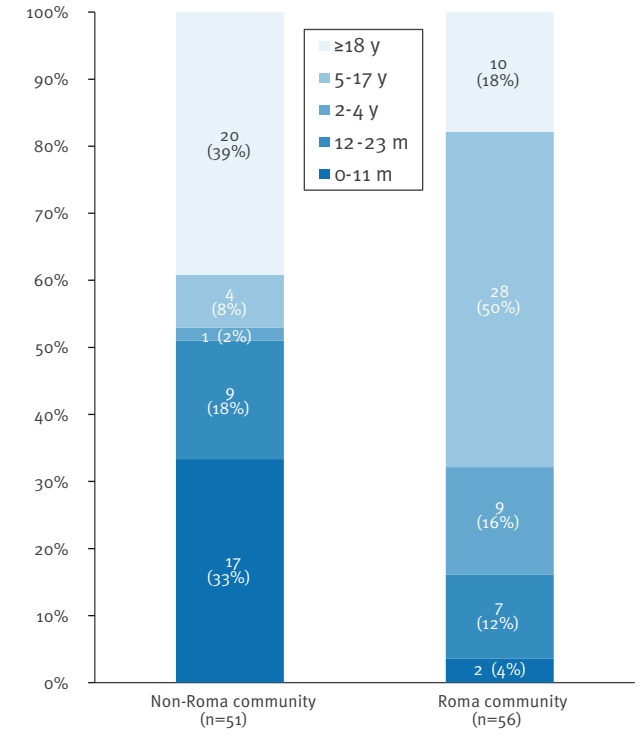
Age distribution of affected Roma and non-Roma in the borough of Hamburg-Mitte measles D4-Hamburg outbreak, 1 December 2008–25 May 2009 (n=216)

A



	Mean	Median	Min	Q1	Q3	Max
Non-Roma community	11,8	1	0	0	24	44
Roma community	10,1	9	0	3,8	15	31

B



A. Boxplot showing mean, median and quartiles of disease onset age of affected Roma and non-Roma community. Figures are given in table below.

B. Stratified age analysis. Cases were assigned to groups as indicated based on age at disease onset.

performed by medical assistants. After arrival of the material at the Institute for Hygiene and Environment, PCR results were available within four to 24 hours and thus proved to be a fast and useful tool for laboratory confirmation of suspected cases found during contact tracing. The Institute for Hygiene and Environment offered PCR analyses free of charge to the public health departments in Hamburg which do not have a budget for laboratory analyses. Furthermore, availability of nasopharyngeal or oral fluid swab material was a prerequisite for genetic comparison of the strains by the NRC and identification of the epidemiological links of the D4-Hamburg virus in Europe [2]. In summary, free-of-charge PCR analyses provided a useful tool for rapid case identification, laboratory confirmation and genetic analysis of the measles strain in the D4-Hamburg outbreak.

Healthcare facilities can play an important role in measles outbreaks [13,14]. This was also true for the outbreak in Hamburg, where an early focus of virus transmission was a waiting area in a hospital, and at least one further transmission site was the waiting area at a doctor's practice. Among the first generation of notified cases a member of hospital staff was identified. Later, a second case of measles in a nurse was notified. Both cases had never received a dose of MCV according to their vaccination cards. The STIKO has since 2007 recommended a single dose of MCV to be given to non-immune healthcare staff, preferably as a combined MMR vaccination [15]. Still there is no obligation to comply with this recommendation and control of adequate vaccination status of their employees is the responsibility of the healthcare facility. Suboptimal immunisation coverage of healthcare professionals in Germany has been described before [16]. The D4-Hamburg outbreak demonstrates again that prevention of disease transmission in healthcare facilities needs to be addressed.

One of the measures to contain the outbreak was a promotional bus positioned in public places on six occasions, providing information and vaccinations. Counselling was requested by 964 visitors who, according to the physicians present, were almost exclusively adults on their way to the nearby shopping centres. Only 18 persons (less than 2% of visitors) accepted on-site MMR vaccination. No data were recorded on age, sex or immunisation status, but it is likely that more visitors with inadequate measles protection did not want to receive a vaccination on this occasion. We conclude that the promotional bus as used in this outbreak was appropriate for providing information on measles to the local public, but it was not efficient in promptly raising vaccination numbers. We would therefore recommend this approach in an outbreak situation where the main intent is increasing public awareness. Furthermore, any outbreak containment measure should record all accessible data in order to allow a later evaluation of the measure's efficiency.

To specifically reach the Roma community, home visits were paid to Roma patients and their household contacts. This approach was chosen because other attempts to establish contact with cases in the community were unsuccessful. As reported by the outbreak investigation teams, initial visits to a household were received with apprehension. On subsequent visits, members of the community stated that this may have been caused by an uncertainty to which public authority the team belonged and what their actual intention was. When a team member identified themselves as a physician they were met with more trust on further visits, and contact tracing and outbreak investigations became possible. During the home visits PCR diagnostics could be offered without delay, which allowed identification of a total of 19 cases that otherwise might not have been notified. Based on information gained during the visits the likely index patient of the outbreak was identified retrospectively and the initial transmission chain in the Roma community could be partially reconstructed. Furthermore, presence of a physician allowed on-site vaccinations in the Roma community. It is a shortcoming that no data were recorded on the number of vaccinations given on these visits, but this measure might have contributed to the fact that virus transmission stopped nine weeks earlier in the Roma community than in the non Roma community of Hamburg-Mitte. In our experience, repeated home visits by a physician are an advisable approach to establish contact to this minority and to take immediate outbreak containment measures.

In a retrospective analysis we compared the age distribution of cases in the Roma community and the non-Roma community in the borough of Hamburg-Mitte. We considered the outbreak parameters as suitable for this comparison for two reasons: (i) number of cases and sex distribution were similar in both groups, (ii) both groups were citizens of the same borough, with 85% living in the same district as demonstrated by postcode analysis. No reliable figures exist on the size of this settled Roma community in Wilhelmsburg, but as an estimate, the community may comprise several hundred persons. It is a shortcoming of our analysis that no statistical reference figures are available to compare age-related incidences in the two subpopulations. Thus, our data only describe case numbers as they were recorded.

The most prominent differences occurred in the strata of 0–11 month- and 5–17 year-olds. In the non-Roma community, 33% of 0–11 month-olds were infected with measles, compared with only 4% of the Roma community. This age group consists of infants too young for MCV immunisation according to STIKO guidelines. Their immune protection correlates with the level and persistence of transferred maternal antibodies and may depend on whether the mother's immunity was acquired by natural infection or by vaccination [17]. Other factors modify this passive immunity, e.g. exposure to wildtype measles virus as a natural booster or

age of the mother during pregnancy [18]. It is tempting to speculate that early protection in the Roma community described here may have been higher because the mothers were exposed to wildtype measles infection, but this hypothesis could only be verified if data on their measles immune status were available.

Only 8% of 5–17 year-olds were affected among the non-Roma citizens, compared with 50% in the Roma community. For this age group standard and catch-up vaccinations including MCV are recommended according to STIKO guidelines. There are two mandatory checkpoints in Hamburg for control of a child's vaccination status by a physician, the first on entry to kindergarten, the second on entry to school. The first checkpoint is unlikely to reach children of a Roma community as they are usually parented by community members. At school entry the main focus is on controlling the vaccination record, and in case of undervaccination the parents are usually referred to their family doctor. This referral might be ineffective with members of a Roma community as they tend to make less use of standard healthcare and preventive services [19-21]. Thus, it is conceivable that the current approach to ensure adequate immunisation status of children in Hamburg is more effective in the non-Roma than the Roma population, in which undervaccinated children and adolescents may accumulate.

In other measles outbreaks in Europe involving Roma communities, the age distribution of cases differed between Roma and non-Roma citizens [22,23], although the results of these analyses are divergent. This might be explained by differences in the subpopulation analysed (e.g. Roma or Sinti), the living conditions of the subpopulation (e.g. settled or travelling), diversity in national vaccination schemes, and different approaches to implement vaccination programmes for underserved minorities.

The group of Roma has suffered extensively from this outbreak in Hamburg and in other European countries [24]. The D4-Hamburg outbreak demonstrates again that strategies to raise measles vaccination coverage should be specifically devised to target underserved populations. Furthermore, innovative outbreak containment measures and vaccination programmes are needed. In a review of the literature concerning the interaction between Roma communities and health service providers, Hajioff and McKee came to the conclusion that published research is sparse [25]. We suggest that studies are needed to better understand the view of Roma community members towards the healthcare sector in order to be able to create vaccination programmes that are acceptable to this neglected minority.

Acknowledgments

We would like to thank Jörg Thyroff, Sabine Richtberg, Veronika Hellmund, Susanne Steinberg from the Public Health Department Hamburg-Mitte and Katharina Traudt, Joachim Kanschik from the Public Health Department Hamburg-Harburg for outbreak investigations. Furthermore we would like to thank Markus Kirchner from the NLGA, Hannover, for information on measles outbreak in Lower Saxony. Finally, we would like to thank Klaus Baumgardt from the Division for Environmental Monitoring, Hamburg, for instruction on geographic information system software. Cartography was based on standard maps from the State Office Geoinformation and Geodetic Survey, Hamburg.

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Quantitative assessment of passenger flows in Europe and its implications for tracing contacts of infectious passengers

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Citation style for this article:
Askar M, Mohr O, Eckmanns T, Krause G, Poggensee G. Quantitative assessment of passenger flows in Europe and its implications for tracing contacts of infectious passengers. Euro Surveill. 2012;17(24):pii=20195. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20195

Article submitted on 03 August 2011 / published on 14 June 2012

In contrast to air travel, there are no recommendations on tracing ground transport passengers exposed to infectious pathogens. We analysed European statistics on passenger transport in different conveyances and conducted expert workshops to discuss environmental conditions in ground transport, indications and minimal datasets required for contact tracing. Transport performance in the 27 countries of the European Union increased from $5.3x10^{12}$ passenger kilometres (pkm) in 1995 to $6.5x10^{12}$ pkm in 2007. Each resident generated on average 13,092 pkm in 2007, of which 2,062 pkm were public ground transport and 1,155 pkm in air transport. In the same year in Germany the total passenger volume in all different conveyances was 67,937 million. Public ground transport accounted for a passenger volume of 11,387 million (16.8%) and air transport for 129 million (0.2%). High efficiency particulate air (HEPA) filtration is frequently used in airplanes but not in ground transport vehicles. Therefore opportunities for disease transmission in public ground transport are not necessarily lower than in air travel. However, contact tracing is rarely conducted in these settings because of immense logistic challenges. Indication for contact tracing should be revisited, including all kinds of passenger transport.

Introduction

A variety of infectious diseases have the potential to spread from one person to the other without the need for direct or intimate contact. In stationary settings such as workplace, school or hospital, persons potentially exposed to a patient shedding an infectious pathogen usually remain within the reach of one local health authority which can trace these contacts to initiate early diagnosis, preventive treatment or hygienic measures to prevent further spread. Travelling in public transport, often in confined spaces, provides opportunities for exposure to and transmission of infectious diseases. It is an established procedure in infectious disease control to trace passengers, with the aim of preventing further spread of a pathogen or providing post exposure prophylaxis or treatment to passengers who had contact on board a vehicle to a fellow passenger or personnel shedding an infectious agent, in the following referred to as contact tracing (CT). CT in public transport settings poses special challenges: exposed passengers usually have a one-time exposure; they do not necessarily live within one health department's jurisdiction and are unlikely to receive information on the exposure other than by direct contact from either the travel company or the health authority since most passenger ground transport vehicles do not use passenger name lists. Announcements via media or other information channels (e.g. social networks) are only rarely used to trace contacts. In public transport conveyances such as airplanes, risk assessment based on documentation of a seating position can facilitate a more focused contact tracing approach.

CT is explicitly addressed in Article 23 of the International Health Regulations from 2005 [1] and has recently led to an amendment of the Decision 2000/57/EC of the European Commission addressing the information exchange between Member States during CT and providing and indicative list of personal data for CT [2]. In both regulations, CT is treated as a control measure which justifies and requires the maintenance of international surveillance and information exchange systems when there is a risk for international disease spread. So far official recommendations from public health institutions and the World Health Organization (WHO) do address CT in air transport, but not explicitly in public ground transport [3-13].

In our work we describe factors that may indicate the need for recommendations in the ground transport setting and try to identify to what extent these might differ from the factors known for air travel. We analysed European statistics on passenger transport in different types of conveyances. Furthermore we report results from an expert workshop that assessed indicators for CT in ground transport conveyances.

Methods

Public ground transport is defined as travelling by the following means of transport: bus/coach, railway or

tram/metro. Public transport in general furthermore includes air and sea transport. Within the framework of the European project 'Response to Emerging infectious diseases: Assessment and development of Core capacities and Tools' (REACT) we conducted two meetings with international experts to identify relevant criteria and indications for CT in public ground transport and a generic minimal dataset for CT [14]. A survey and round table discussions determined infectious diseases pertinent to CT. Moreover, relevant environmental conditions and results of the passenger transport data analysis were discussed. Participants of the meetings were experts working in or for local and national public health departments, the International Association of Public Transport (UITP), and the WHO.

European passenger transport

Eurostat and the European Commission Directorate General for Energy and Transport provided the latest summarised European passenger transport statistics from 1995 to 2007 [1,15]. Each EU Member State reports statistical data on passenger transport in the form of passenger transport performance (TP), which is defined as the number of passengers multiplied by travelled distance and measured in passenger-kilometres (pkm). TP is reported based on the territoriality principle, i.e. only the TP within the territory of the reporting country is considered. We analysed TP for different types of transport within the 27 European Union Member States (EU-27) specifically for transport by passenger car, powered two-wheeler, bus/coach, railway, tram/metro, air, and sea transport.

German passenger transport

As the core research group was located in Germany, we used the data from Germany for the detailed analysis and comparison. We received statistical data on total number of passengers, TP, short- and long-distance travel by bus/coach and railway, and information on the average travel distance in the period 2004 to 2007 from the German federal statistical office (DESTATIS) and from the German Institute for Economic Research (DIW) [16-19].

In Germany, passenger transport by bus/coach and tram/metro is reported as public road transport. Short distance traffic by bus is defined as travel on public suburban and metropolitan commuter transport with the majority of passengers travelling less than 50 km or for less than one hour. Accordingly, in long-distance bus travel, the majority of passengers is travelling more than 50 km, or for more than one hour.

Regarding transport by railway, the definition of short- versus long-distance travelling depends not only on the distance travelled (limited up to 50 km or more than 50 km), but in some cases also on the type of conveyance. For instance, travel by high speed trains is always reported as long-distance transport, even when the travelled distance might be less than 50 km [18].

Environmental conditions in ground transport conveyances

In order to gather information on environmental conditions that may influence the risk of disease transmission in public ground transport, we conducted a literature research on technical systems such as air conditioning and ventilation used in buses/coaches and trains.

In January and February 2009, we conducted a scientific literature search on technical systems in relation to airborne transmission of infectious diseases in public ground transport using the SCOPUS database (the largest scientific database currently available). The search was conducted using a combination of keywords from three groups that were connected by 'AND'. The first group contained the following keywords: air condition, air filter, seating distance, and ventilation. The second group contained: transmission, infectious, airborne, droplet, disease, and the third group contained: means of transport, conveyance, bus, coach, railway and train. In July 2011, the literature search was updated. The search results were screened for relevance with regard to transmission of airborne infectious disease in public ground transport by two REACT researchers.

Furthermore, we contacted by email and telephone (national and Europe-wide) coach and railway transport companies and organisations as well as two internationally operating rail equipment manufacturing companies and a university research group focusing on airflows in confined spaces, in order to gather information on technical systems used in different means of transport in Europe. In addition, environmental conditions potentially relevant for CT were discussed in the REACT expert meetings.

Indications for CT in public ground transport

In the REACT expert meetings we discussed pathogens and indications that could be relevant for risk assessment and decision making for CT in public ground transport, as well as the logistical challenges of conducting CT in various means of transport.

Minimal dataset for CT

The passenger locator card is a paper form available on board of aircrafts. It provides a method to rapidly collect passenger contact information and is recommended to be used when public health authorities suspect the potential for disease transmission on board of an aircraft and a subsequent need for contact tracing. It was developed by an informal transport working group convened by WHO [12]. The group consisted of representatives from national public health authorities and international transport organisations.

Annex III of Decision 2000/57/EC includes an indicative list of personal data to be collected and shared between EU Member State authorities for the purpose of CT. This list mirrors to a large extent the information to be filled in the 2009 WHO passenger locator form

[12] and includes the passenger's name, sex, date of birth, telephone numbers, email and home addresses as well as temporary addresses (called contact information in Annex III) and emergency contact details. In addition to the passenger locator form, Annex III also contains questions on nationality, type of identity document (ID), ID number and issuing authority.

We compared the 2009 draft version of the passenger locator card [12] with the 'indicative list of personal data for the purpose of contact tracing' in Annex III of the 2009 amendment of the 2000/57/EC Decision of the European Commission [2]. A minimal dataset required for CT was also part of the discussion at the REACT expert meetings.

Results

European passenger transport

Within the EU-27, passenger transport performance (TP) increased from $5.3x10^{12}$ pkm in 1995 to $6.5x10^{12}$ pkm) in 2007. On average each habitant of the EU-27 generated about 13,092 pkm in 2007. Public ground transport (bus/coach, railway, and tram/metro) accounted for an average TP per EU-27 habitant of 2,062 pkm and air transport for 1,155 pkm. TP by air transport had a growth rate of 4.5% from 1995 to 2007 while TP for all other passenger transport types had a growth rate of less than 2% (Figure).

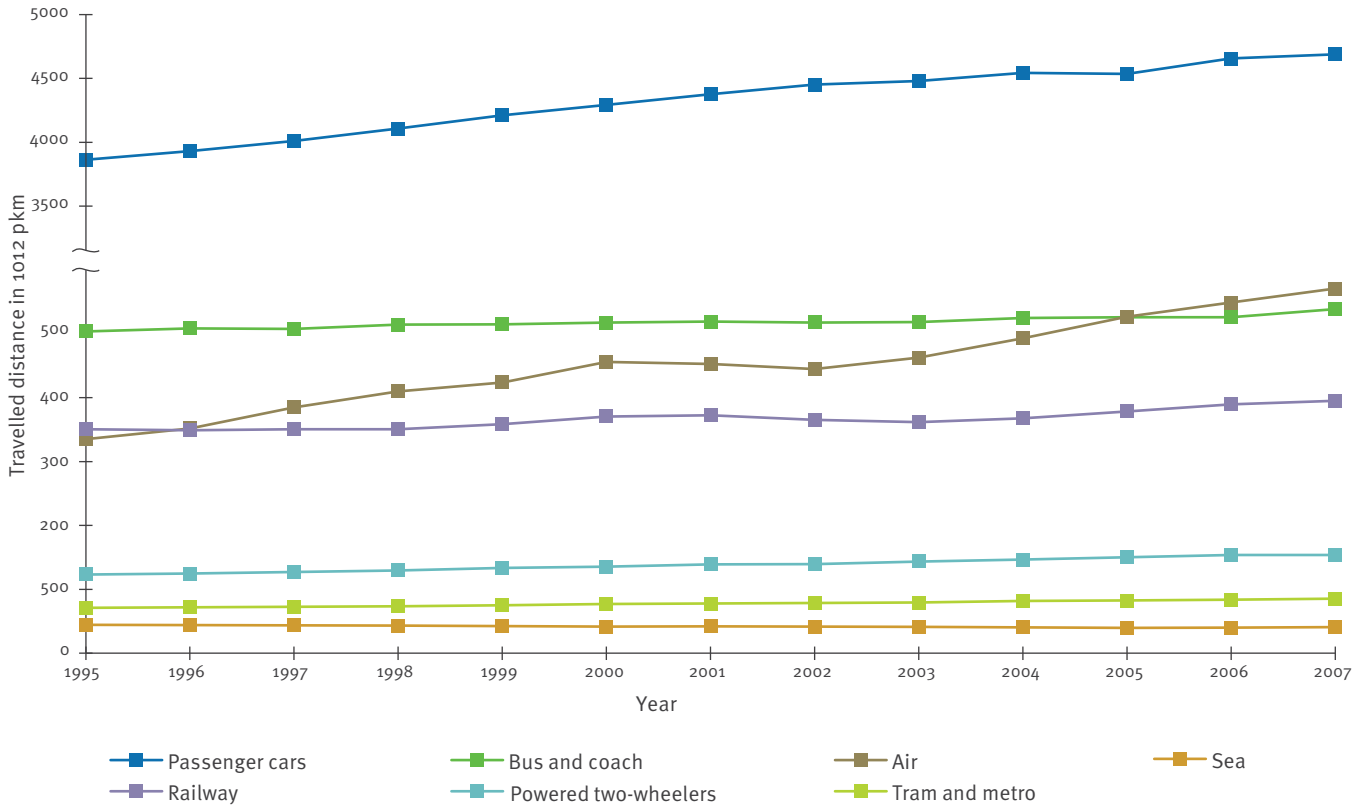
In 2007, the share of total TP was 74.8% ($4,842x10^9$ pkm) by private transport (passenger car and powered two-wheeler), 8.8% ($571x10^9$ pkm) by air, 8.3% ($539x10^9$ pkm) by bus/coach, 6.1% ($395x10^9$ pkm) by railway, 1.3% ($85x10^9$ pkm) by tram/metro and 0.6% ($41x10^9$ pkm) by sea transport. Hence, all public ground transport (bus/coach, railway, tram/metro) generated a share of 15.7% of the total TP of $6,473x10^9$ pkm in the EU in 2007.

German passenger transport

In Germany public ground transport generated a share of 14.6% ($161.5x10^9$ pkm) and air transport a share of 5.3% ($59x10^9$ pkm) of the total German TP in 2007. In the same year the number of passengers (passenger volume) transported by public ground transport generated a share of 16.8% (11,387 million passengers) and air transport a share of 0.2% (129 million passengers). Compared to 2004, railway and air transport generated a higher TP in 2007. However, the share of passengers travelling by air remained at a low level of 0.2% (see details in Table 1).

Figure

Passenger transport performance by mode of transport in passenger kilometres, EU-27, 1995–2007



pkm: passenger kilometers.
Source: [1].

Table 1

Passenger volume and passenger transport performance of different means of transport, Germany, 2004 and 2007

	Year	Private transport	Public ground transport		Air	Total
		Passenger car and Powered two-wheeler	Public road transport (Bus/coach and Tram/metro	Railway		
Passenger transport performance (in billion pkm)[a]	2004	887 (81.3%)	83 (7.6%)	73 (6.7%)	48 (4.4%)	**1,091**
	2007	885 (80.1%)	82 (7.4%)	79 (7.2%)	59 (5.3%)	**1,106**
Passenger volume (in million)[a]	2004	57,275 (83.6%)	9,057 (13.2%)	2,091 (3.1%)	106 (0.2%)	**68,529**
	2007	56,420 (83.0%)	9,146 (13.5%)	2,241 (3.3%)	129 (0.2%)	**67,936**

[a] Passenger transport performance is given in billions (x10^9); Passenger volume is given in millions (x10^6).

Table 2

Passenger transport performance, passenger volume and average travelled distance in short- and long-distance transport by bus/coach and railway, Germany, 2004 and 2007

Year	Short-distance transport[b]			Long-distance transportc			Total passenger TP[a] (in billion pkm)	Total passenger volume[a] (in million)
	Passenger TP[a] (in billion pkm)	Passenger volume[a] (in million)	Average trip distance (in km)	Passenger TP[a] (in billion pkm)	Passenger volume[a] (in million)	Average trip distance (in km)		
2004	75 (68.8%)	7,213 (98.4%)	13.6	34 (31.2%)	121 (1.6%)	290.5	109	**7,334**
2007	81 (69.6%)	7,374 (98.4%)	14.1	35 (30.4%)	121 (1.6%)	393.6	116	**7,495**

TP: transport performance.

[a] TP is given in billions (x10^9); Passenger volume is given in millions (x10^6).

[b] Short-distance transport: travel distance ‹50 km.

[c] Long-distance transport: travel distance › 50 km or transport in predefined conveyances such as high speed trains.

About two thirds (69.6%) of the TP and 98% of passenger volume in ground transport were generated by short-distance travel in Germany in 2007 (Table 2). In comparison with the data from 2004, the average trip distance for long-distance transport by bus/coach and railway increased by 26%.

Environmental conditions in ground transport conveyances

The scientific literature search resulted in around 1,600 hits. After screening of title and abstract, 11 potentially relevant publications were identified and the full text article read. Finally, six articles addressing environmental conditions and possible airborne infectious disease transmission in public ground transport in busses and trains were selected [20-25]. Four of the six articles were published in 2010 or later, the other two in 2000 and 2007. Five identified articles described results of Computational Fluid Dynamics (CFD) models simulating the risk of airborne infection in public ground transport by investigating the microenvironmental conditions or characteristics of the dispersion of expiratory droplets and droplet nuclei in public busses or trains. Two articles assessed the pathogen-specific transmission risk for influenza [22,25], one article the risk for *Mycobacterium tuberculosis* [20]. Another study validated the results of its CFD model by monitoring the quality of the indoor environment on the Harvard University shuttle bus [21].

According to the models, air distribution method, ventilation rate, exposure time and seat arrangement/seating position (in terms of proximity) affected the risk of transmission of airborne infectious diseases on buses and trains [22,25]. Air circulation mode with displacement ventilation method or high efficiency filtration was found to reduce the infection risk [22]. The study published by Furuya in 2007 assessed the influence of environmental parameters by varying the duration of exposure and the number of passengers [25]. A mathematical model based on the Wells-Riley model was used including the reproduction number R_A for influenza infection on a train. According to the results the exposure time was found to increase the risk linearly.

In addition, the number of passengers also increased the risk, whereas doubling the rate of ventilation limited the transmission risk by reducing the estimated reproduction number for influenza in the vehicle [25].

The sixth article describes two surveys of commercial transportation including aircrafts, interstate busses, short-distance commuter trains and subways, which were conducted in 1994 and 1996 [24]. Beside other environmental measurements such as carbon dioxide (CO_2), surface dust was collected using handheld vacuum cleaners, sifted, and fine particles analysed for bacteria. Although the total concentration (in colony-forming unit/m^3) of airborne bacteria was not statistically different across the various travel modes (except for samples taken inside the aircraft cabin during deboarding); the highest geometric mean concentration of bacteria in ground travel was found in subways, followed by trains. However, the authors point out that identification of bacteria and detection of viruses important for evaluating the respiratory infectious risk were not performed [24].

Of six contacted transport organisations and companies, one internationally operating transport organisation agreed to share information on the technical properties of air conditioning systems in public ground conveyances. According to this information, HEPA-filters are not used at all in ground conveyances. In addition, due to the technical diversity within the vehicle fleet, technical equipment such as ventilation systems and seating arrangements in ground conveyances may differ significantly even within one transport company. Based on information of one company high-speed trains used for long-distance travel in most EU-countries often use coarse dust filters (G4-filter/EU 4-filter) [26] to remove particles above 10 µm.

The REACT experts concluded that environmental parameters do have an effect in the risk of transmission of infectious disease from one passenger to another in public ground transport. While the duration of exposure and proximity to other passengers are seen as important parameters in assessing the risk of disease transmission, little is known about the influence of technical parameters such as ventilation systems in ground conveyances on transmission. Even though simulation models demonstrate the potential influence of different environmental conditions on the risk of airborne disease transmission in public ground transport, evidence from experimental and microbial investigations in real events is still insufficient. Furthermore the experts agreed that access to information on environmental conditions and the wide range of technical features is limited. In addition, the assessment of such technical information with regard to risk of infectious disease transmission in public transport is challenging for health professionals.

Indications for CT in public ground transport

The REACT experts agreed that consideration for CT in ground transport should follow the same principles as in air travel. Overall, the judgement was that even though scientific evidence is lacking, the chance for transmission of infectious disease from one passenger to another in public ground transport might be the same as on airplanes. It was acknowledged that in public ground transport there is often no documentation in place to identify passengers with the exact seating position which makes it impossible to trace passengers individually. Furthermore, public ground transport often works without passenger attendants, making it more difficult to implement the system of passenger locator cards.

During two expert meetings and two round table discussions the REACT experts agreed to exclude food-borne and vector-borne pathogens as indications for CT. They concluded that CT should generally be considered in situations with the following diseases: pulmonary tuberculosis, meningococcal disease, viral hemorrhagic fever, Lassa fever and measles [14]. Important factors influencing their decision were their personal experience concerning the feasibility of CT in various settings, the severity of an infectious disease, its infectiousness, and the possibility of providing an effective therapy after tracing contact persons.

Minimal dataset for contact tracing

The experts of the REACT project suggested that, in order to work towards integrated surveillance systems, a minimal data set for CT in public ground transport should require similar data as recommended for CT in air transport. It was agreed that the items requested in the locator form in its updated version cover all and even more than the essential information necessary to potentially initiate CT.

Discussion

Public ground transport in the EU covers more travel than air transport. In Germany TP is nearly threefold, and passenger volume nearly 90-fold higher for ground transport as for air transport. Although the data do not allow the computation of person travel time, these figures indicate the importance of exposure during travel in public ground transport compared to air travel. However, we cannot exclude that short-time exposure may not be important in the transmission of infectious diseases in public ground transport. Furthermore there is evidence that cumulative exposure in repetitive short trips can lead to disease transmission, e.g. reports on cases of TB transmission on school busses [27-29].

Duration of exposure, however, is only one suspected influence on the risk of person to person transmission [30]. For pathogens transmitted by droplets the proximity and the interaction between two passengers plays a role [30-33] and may not differ between ground and air travel as long as individual seating is available for

all passengers. For airborne pathogens the type of air ventilation system may have a relevant impact on how long infectious particles will persist in the air [23,34-36]. As documented for tuberculosis, droplet nuclei particles may be transported through ventilation systems [37] and remain suspended and viable in the air over a period of time [38-41].

Some air filter systems with a cut-off of 0.3 µm are capable of removing airborne bacteria such as *Mycobacterium tuberculosis*. These HEPA filters are used in most aircrafts on flights within the EU [42,43] but not in busses/coaches, trains or tram/metro. Some modern high-speed trains are reported to use coarse dust filters which would not limit the spread of certain airborne pathogens, such as *Mycobacterium tuberculosis*. Ground transport therefore provides a more favourable environment for airborne transmission.

Given that the frequency of potential exposure and the environmental conditions are comparable, the reason why CT is less regularly conducted in public ground transport is likely to be the result of logistic challenges rather than lower risk for transmission. Indeed, even when passengers have assigned seating positions, ground transport companies have more difficulties in making passenger contact information available for CT as no passenger-related data is stored.

However, various airlines have abandoned passenger-specific seat assignments and thus cannot provide seat-specific passenger data at all. This lead to the concept of passenger locator forms, filled in by the passengers themselves [12]. These forms have been used in situations where a potential disease transmission has already been identified during the flight, and passenger attendants were able to hand the passenger locator forms as they leave the plane [12]. In ground transport this approach seems not feasible for practical reasons, e.g. because of higher flexibility and less documentation regarding itinerary and seating.

In comparison to the 2009 passenger locator form [12], Annex III of the amended Decision 2000/57/EC also contains questions on nationality, ID type, ID number, and issuing authority [2]. We believe these data are unnecessary and possibly problematic from the point of view of data confidentiality. At least in Germany the legal framework does not authorise health departments to use passports for patient identification, nor does it allow involving police authorities to use these data to identify or find a contact person. While legislation in other countries may not be so restrictive, it seems unnecessary to request ID numbers in such a context. Whatever strategy is chosen to identify and locate exposed passengers, the information collected in the WHO passenger locator form appears sufficient to the REACT experts with respect to possibilities to contact passengers, and the additional suggestions in Annex III of the amended Decision 2000/57/EC [2,12] may cause more legal concerns than additional benefit.

All relevant issues considered, individual CT of passengers in ground transport seems only feasible in cases where contacts are known by other circumstances, e.g. a school outing by bus or train [44]. One way of identifying possible contacts of an ill passenger is to involve the mass media. However, a public call for contacts may cause unnecessary anxiety among passengers who are not at risk and might at the same time miss the attention of co-travellers who are at risk. Nevertheless, in case of exposure to a very severe disease, this approach may be considered.

Modern Internet-based technologies offer an option of posting announcements related to possible transmission of infectious diseases during travel. Coded secure access to the passengers who travelled on a particular occasion might stimulate a better response as many data confidentiality concerns would be resolved. The acceptance of these alternative systems can be further investigated with participation of relevant stakeholders and in view of the data presented here.

The presented EU data refer to figures published in 2009. These were the most recent data we were able to use. Due to the delay in data collection, the data always seem to be outdated by two years. However, the trends described seem to be stable over time.

The transport statistics presented here give only a limited view on the likelihood of infectious disease transmission on board of public transport conveyances partly because of the territorial principle of data collection. More importantly, the duration of the trip as a commonly described proxy for risk of infection [4,45-49] is not measured. Furthermore, data on passenger volume for the different means of transport are not available for the 27 EU Member States.

Within the scope of this study, we could analyse in detail the data from one EU country only, Germany. However, the transport data is well comparable to the most populous EU countries (France, Italy and the United Kingdom) and the conclusions might also be applicable for the other EU countries.

Even taking into account the limitations of our assessment we showed that the risk for infectious disease transmission is comparable between ground and air transport. Logistical difficulties in implementing CT in ground transport raise the question of whether more efforts are needed to reinforce ground transport CT or rather whether the established way of conducting CT in air transport should be reviewed. We therefore suggest that the indications for CT should be revisited in general terms.

Acknowledgments

We thank the following experts and colleagues for sharing their knowledge and judgement for this work: Philip Monk (HPA, Local and Regional Services, UK), Corien Swaan (RIVM, Netherlands), Udo Goetsch (Frankfurt Department of Health, Germany), René Gottschalk (Frankfurt Department of Health, Germany), Daniel Menucci (WHO-Office IHR, France) and Lindsey Barr (International Association of Public Transport, Belgium).

This publication arises from the project REACT which has received funding from the EU, in the framework of the Public Health Programme (funding number 2007211).

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ECDC public health response to the threat of resistant gonorrhoea in Europe

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Citation style for this article:
Van de Laar M. ECDC public health response to the threat of resistant gonorrhoea in Europe. Euro Surveill. 2012;17(24):pii=20196. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20196

Article submitted on 12 June 2012 / published on 14 June 2012

The European Centre for Disease Prevention and Control (ECDC) has launched its public health response plan to control and manage the threat of resistant gonorrhoea across Europe [1]. This is the first regional response plan after the World Health Organization (WHO) warned about drug-resistant gonorrhoea becoming a major public health challenge [2].

Gonorrhoea poses a serious public health problem as it has developed resistance to several antibiotics and is becoming less susceptible to the last available antibiotics (third-generation cephalosporins).

Results from the European gonococcal antimicrobial surveillance programme (Euro-GASP) show that the percentage of isolates with decreased susceptibility to the recommended drug for treatment of gonorrhoea (cefixime) rose from 4% in 2009 to 9% in 2010. Decreased susceptibility was detected in 17 countries in 2010, seven more than in the previous year. At the same time, the susceptibility to the injectable drug ceftriaxone is decreasing as well [3]. The loss of both cefixime and ceftriaxone as treatment options for gonorrhoea would have a significant impact on public health: gonorrhoea is the second most commonly reported bacterial sexually transmitted infection (STI) in Europe [4] and its effective control relies entirely on antimicrobial treatment.

To this respect, ECDC launched a public health response plan that has been developed in collaboration with an expert group, including STI microbiologists and the International Union against STI. The goal of the plan is to minimise the impact of resistant gonorrhoea in Europe with the following components:

- strengthening the surveillance of gonococcal antimicrobial susceptibility in European Union/European Economic Area (EU/EEA) Member States to inform national treatment guidelines (including training courses);
- ensuring that a minimum capacity for culture and susceptibility testing at national level in EU/EEA Member States is available or developed;
- establishing a strategy to rapidly detect patients diagnosed with gonorrhoea that experience a clinical treatment failure;
- outlining a set of recommended public health actions at the national level following the detection of resistant cases.

The current level of decreased susceptibility against cefixime is of great concern and it is likely that more treatment failures will be reported. Public health experts and clinicians need to be informed about the current critical situation and should be vigilant for treatment failures.

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