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Preparedness is crucial for safe care of Ebola patients and to prevent onward transmission in Europe – outbreak control measures are needed at its roots in West Africa

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Recent events related to the current outbreak of Ebola virus disease (EVD) in West Africa seemingly indicate inevitable problems that Europe has to face: an individual became symptomatic from Ebola virus disease only after having arrived in a non-affected country [1], and healthcare workers became infected with Ebola while caring for patients, either in West Africa or in non-affected countries where they had been medically evacuated [2–4]. Moreover, media enquiries and reports reveal concern among the general public.

All this follows the dramatic development of the epidemic in West Africa over the past months, and forecasts unanimously agree that it will take weeks if not months before the trend in the affected region can be inverted and the epidemic be controlled [5–6]. Therefore, European countries will have to cope with more cases arriving from affected areas while being well prepared to prevent secondary transmission.

While infections in the dedicated healthcare settings in Europe will probably remain single and unfortunate events, they need to be investigated thoroughly in order to incorporate the lessons learnt from them into improved standards and procedures as well as consider them in training activities.

There are three possible scenarios that may result in patients infected with Ebolavirus to present in healthcare settings in Europe and healthcare workers or support staff coming into contact with them.

The first scenario is related to a patient in an affected country with a confirmed Ebolavirus infection who is medically evacuated to Europe. This scenario should not result in further transmission in Europe and thus constitute a rather low risk as preparations are possible for such planned situations. However, as pointed out above, and whenever humans are involved, occasions may occur where unfortunate events may lead to infection of a healthcare worker contact. While caring for Ebola patients in European settings should remain safe when appropriate procedures are in place, a 100 per cent elimination of risks can never be expected.

The second scenario refers to a symptomatic patient boarding a commercial flight, possibly to seek medical care in Europe. Upon declaring the Ebola outbreak in West Africa a public health event of international concern, the World Health Organization (WHO) International Health Regulations Emergency Committee also recommended exit screening in the affected countries [7]. To render this seemingly easy and not too cost intensive measure effective, it needs to be applied systematically to all travellers departing from affected countries. Where this is the case, the risk of exportation can be minimised to a great extent. The support provided by the United States in the affected countries should have helped in the current situation in this respect [8]. Additional screening at the point of entry (entry screening) may complement exit screening, as it may detect the few symptomatic cases that could have been missed by the exit screening or those who may have become symptomatic during the flight. However, entry screening is complex to implement because of the indirect routes that may be taken by travellers.

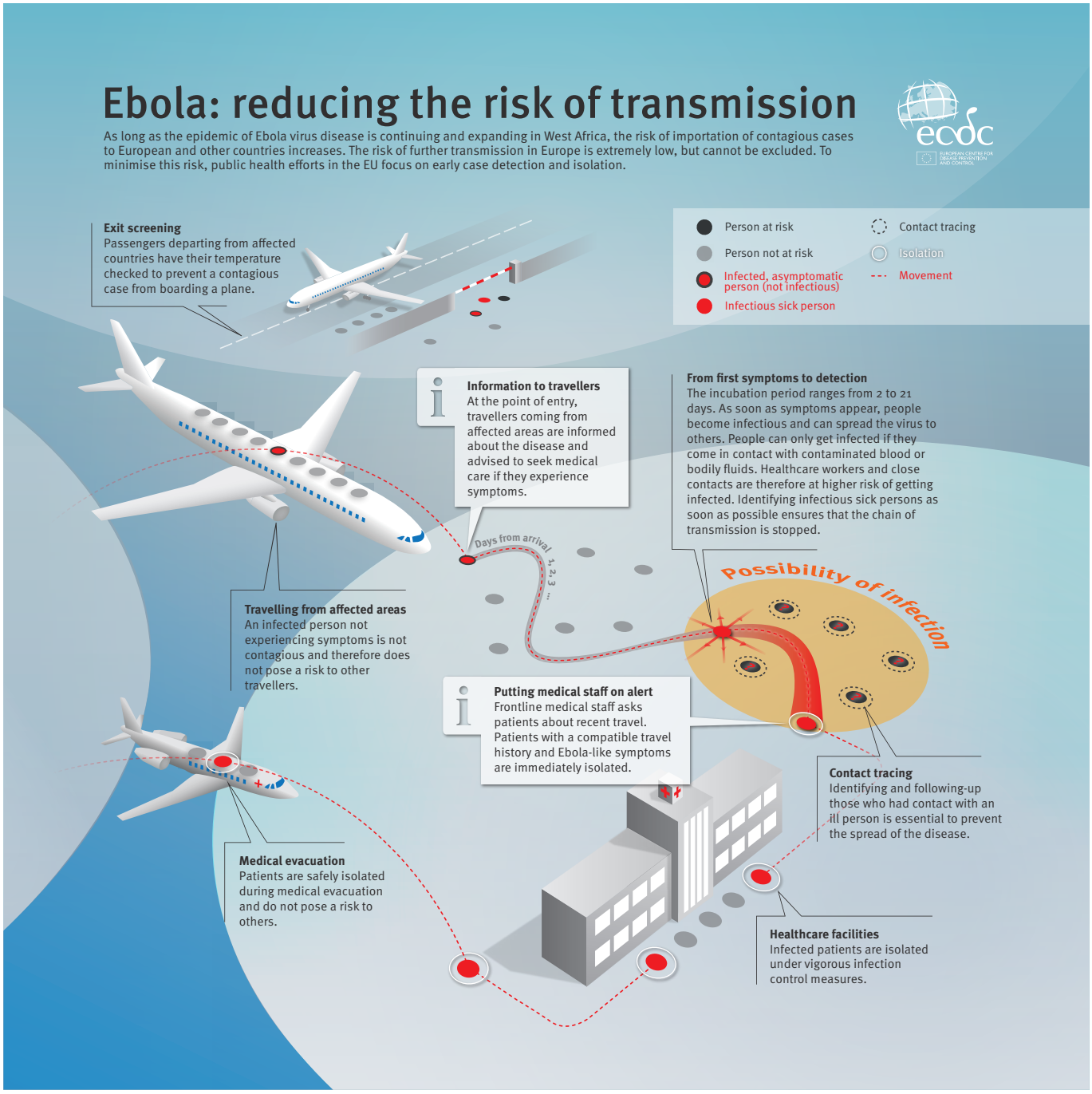
The third scenario consists of a person travelling to Europe from an affected country while incubating the virus and developing symptoms only after arrival, as experienced recently in Dallas, United States [1]. This situation constitutes the greatest risk to Europe and predisposes to limited secondary transmission to close contacts at the early stage of the disease, when the patient becomes infectious and before being isolated. Efforts are made by all countries in the European Union to minimise this risk through a set of measures namely (i) to provide information about the disease and advice in case of symptoms to all travellers coming from affected areas, (ii) to sensitise front-line healthcare providers about possible EVD symptoms and the need to enquire about recent travel to the affected region

while ascertaining patients, and to ensure their timely isolation when EVD is considered, and (iii) to provide guidance for investigating cases and for infection control measures that should allow to care safely for such patients.

The infographic presents in a simplified way three scenarios described above (Figure).

Medical evacuations to Europe remain particularly safe when infection control measures are applied by experienced, well trained professionals. Despite the envisaged increase in such evacuations that will eventually result in treatment of Ebola cases in European hospitals, transmission to healthcare personnel should remain the unfortunate sporadic exception. More cases as seen in Dallas will be seen in Europe. Any such situation could happen as well in other regions of the world.

Above all, however, the cases of recently evacuated infected healthcare workers to Europe who were involved in responding to the outbreak in affected countries, should remind us about the important work of those who work in West Africa where the burden of EVD weighs heavily on the population and has affected local healthcare structures and other services considerably. The risk of further spread associated with the ongoing Ebola outbreak in West Africa can only be mitigated by controlling the epidemic at its roots in the affected countries.



We are in tune with voices raising concern about the current situation and calling for strong leadership within the international community to ensure that adequate measures are implemented in this critical situation [9]. The European Centre for Disease Prevention and Control (ECDC) strongly supports respective initiatives from WHO as far as possible within its mandate. As pointed out in the Lancet [9], currently, the international community needs to further strengthen its support to affected countries. While it is still unclear when the outbreak will end, it will be important to analyse this event carefully and learn from it in order to be better prepared for similar events in the future. This we owe to those who suffer and who lost their lives as well as those who are working to save lives and trying to contain this unprecedented Ebola outbreak in the affected countries.

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Describing readmissions to an Ebola case management centre (CMC), Sierra Leone, 2014

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Case management centres (CMCs) are part of the outbreak control plan for Ebola virus disease (EVD). A CMC in Sierra Leone had 33% (138/419) of primary admissions discharged as EVD negative (not a case). Fifteen of these were readmitted within 21 days, nine of which were EVD positive. All readmissions had contact with an Ebola case in the community in the previous 21 days indicating that the infection was likely acquired outside the CMC.

Between 26 June and 1 September 2014, 138 patients were discharged from the Kailahun Ebola case management centre (CMC) in Sierra Leone, as non-Ebola virus disease (EVD) cases, because they tested negative for the virus by polymerase chain reaction (PCR). Of these, 15 returned to the CMC within 21 days of their first admission and subsequently nine tested positive for Ebola virus. This raised the question as to whether CMCs could be acting as potential amplifiers of infection even though appropriate infection control measures are being followed. Such a question is of public health importance to the overall future control of the EVD outbreak, which is ongoing in West Africa [1]. To our knowledge, there is no literature available which describes the evolution of readmissions to Ebola CMCs during an outbreak and this paper addresses that deficit.

Ebola virus disease outbreak in West Africa

The current EVD outbreak in West Africa commenced in Guinea in December 2013 [1] and since then has spread to Sierra Leone, Liberia, Nigeria and Senegal [2]. It is the largest EVD outbreak recorded in history [2] with 6,553 (suspected, probable and confirmed) cases and 3,083 deaths reported as of 23 September 2014 in affected countries [2]. The World Health Organization (WHO) declared the outbreak a public health emergency of international concern on 8 August 2014 [3].

During EVD outbreaks transmission via infected body fluids occurs in three settings: (i) community, through contact with an infected person or contaminated fomites, (ii) burials, due to touching dead bodies, and (iii) nosocomial, via lack of infection control measures within healthcare facilities. In particular, the latter two settings [4] can quickly amplify an Ebola epidemic [5,6]. The incubation period of the virus ranges from two to 21 days [5,7].

Description on the Kailahun Ebola case management centre

Médecins Sans Frontières (MSF) have six Ebola CMCs operational in West Africa, one of which is based in Kailahun, Sierra Leone. Suspected, probable and confirmed case definitions are equivalent to those used by the WHO [8]. In brief, a suspected case is any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a person with suspected, probable or confirmed EVD or with a dead or sick animal; any person with sudden onset of high fever and at least three of the following symptoms: abdominal pain, anorexia, arthralgia, diarrhoea, dysphagia, dyspnoea, headache, hiccupping, lethargy, myalgia, or vomiting; or any person who had unexplained haemorrhagic symptoms or who died suddenly from an unexplained cause. A probable case is any person suspected to have EVD who was evaluated by a physician or any person who died from suspected EVD and had an epidemiological link with a confirmed case but was not tested and did not have laboratory confirmation of the disease. Suspect or probable cases are classified as confirmed when they had a positive laboratory test for EVD.

The Kailahun CMC (KCMC) is divided into a high risk zone and a low risk zone (Figure 1). The low risk zone includes the medical and nursing administrative tents, laundry area, storage area and other necessary facilities to support the high risk zone. Within the high risk zone personal protective equipment (PPE) must be worn at all times. The high risk zone comprises: a suspected cases ward, a probable cases ward and eight confirmed cases wards. A barrier fence separates the

confirmed cases wards from the suspected and probable cases wards preventing patient interaction between these two types of wards.

Following medical assessment in triage, patients are referred to the suspected or probable cases ward depending on their case classification. An EVD PCR test (developed in-house by the Public Health Agency of Canada) on a blood sample is then performed. If this is positive the patient is transferred to the confirmed cases ward for further medical support while a negative result allows the patient to be discharged from the CMC. When a patient has a negative PCR result but symptom duration of less than 72 hours, a repeat PCR test is performed at 72 hours or more of symptoms to rule out a false negative result [9]. A patient can spend from less than 24 hours up to three days in the suspect/probable section of the CMC while awaiting the exclusion or confirmation of EVD. When PCR negative patients are discharged, they are considered exposed, and are added to the contact list. Patients who are discharged negative for EVD (not a case) from the suspect/probable wards have the potential to be readmitted at a later date, and test either positive or negative for EVD. When readmissions test positive, they can cause anxiety among medical staff as they try to decipher if the patients have had any other EVD contact history apart from their previous primary assessment in the CMC.

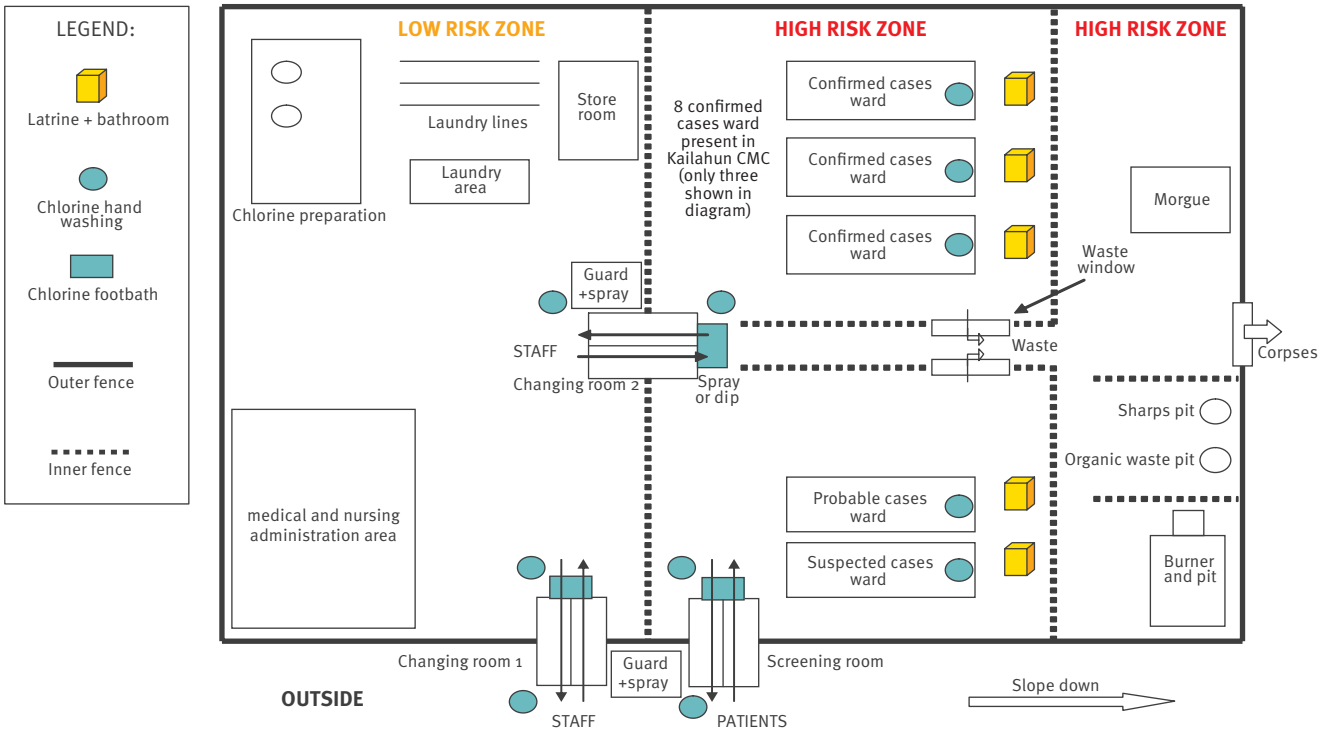
Collection of readmission data at the Kailahun Ebola case management centre and data analyses

A patient register is maintained at the KCMC. It contains basic demographic, epidemiological, medical, laboratory and outcome data for each patient admitted to the facility in Excel 2010 format. All data are stored in a secure manner. To be classified as a readmission a patient must have at least two admission episodes to the CMC that have identical first name, surname, age, sex and address information. All patient readmissions since 26 June 2014 with their corresponding original admissions were extracted from the database. No time limit was imposed on the interval between admission and corresponding readmission when selecting cases. Outcomes for patients were classified as one of the following: cured, dead or not a case. Cured patients had been admitted with a positive EVD PCR and ultimately discharged alive with a negative EVD PCR. Patients classified as dead, had a positive EVD PCR at admission and subsequently died in the CMC from EVD-related complications. The not a case outcome referred to patients who were admitted to the suspect or probable wards, tested negative for the virus by EVD PCR and were then discharged from the CMC.

The crude readmission ratio (CRR) was calculated as the total number of readmissions as a proportion of all *'not a case'* primary discharges. Furthermore, the positive readmission ratio (PRR) was defined as the number

Figure 1

Outline map of Médecins Sans Frontières (MSF) Ebola case management centre (CMC)



Source: Sterk E. Filovirus haemorrhagic fever guideline. Geneva: Médecins Sans Frontières; 2008.

of readmissions with a positive EVD PCR as a proportion of all *'not a case'* primary discharges.

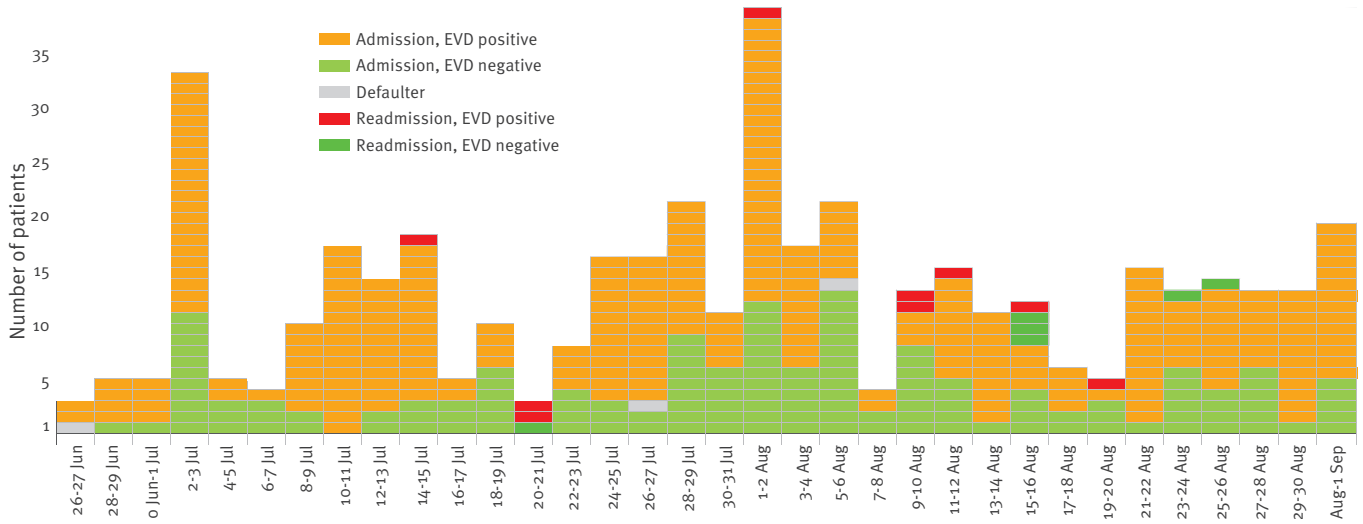
This study fulfilled the MSF Ethics Review Board (Geneva, Switzerland) approved criteria for analysis of routinely collected anonymous programme data. All activities conducted by MSF were approved by the national authorities of Sierra Leone.

Results

Between 26 June and 1 September 2014 (study period), there were 419 primary admissions at the KCMC. Of these, 278 (66%) were EVD PCR positive and 138 (33%) were EVD PCR negative. Three (‹1%) admitted patients did not stay long enough in the centre to be tested for EVD (defaulters). During the same period there were 16 readmissions at KCMC. One readmission was

Figure 2

Distribution of readmissions to the Ebola case management centre (CMC), Kailahun, Sierra Leone, 26 June–1 September 2014 (n=15 readmissions)



EVD: Ebola virus disease.

Table 1

Primary admission and corresponding readmission outcomes, Ebola case management centre (CMC), Kailahun, Sierra Leone, 26 June–1 September 2014 (n=15)

Patient number	Primary admission				Secondary admission (readmission)			
	Time between symptom onset and admission	LOS	EVD PCR result	Outcome	Time between symptom onset and admission	LOS	EVD PCR result	Outcome
1	Unknown	2 days	Negative	Not a case	Unknown	22 days	Positive	Cured
2	0 day	3 days	Negative	Not a case	2 days	5 days	Positive	Death
3	1 day	2 days	Negative	Not a case	1 day	3 days	Negative	Not a case
4	1 day	2 days	Negative	Not a case	1 day	7 days	Positive	Death
5	8 days	1 day	Negative	Not a case	1 day	4 days	Negative	Not a case
6	2 days	2 days	Negative	Not a case	1 day	14 days	Positive	Death
7	3 days	1 day	Negative	Not a case	3 days	21 days	Positive	Cured
8	1 day	3 days	Negative	Not a case	3 days	2 days	Positive	Death
9	9 days	3 days	Negative	Not a case	2 days	23 days	Positive	Cured
10	0 day	2 days	Negative	Not a case	6 days	2 days	Negative	Not a case
11	3 days	1 day	Negative	Not a case	4 days	Current inpatient	Positive	Current inpatient
12	3 days	1 day	Negative	Not a case	1 day	7 days	Positive	Death
13	5 days	6 hours	Not performed	Defaulter	4 days	1 day	Negative	Not a case
14	1 day	3 days	Negative	Not a case	3 days	1 day	Negative	Not a case
15	1 day	2 days	Negative	Not a case	1 day	3 days	Negative	Not a case

EVD: Ebola virus disease; LOS: length of stay; PCR: polymerase chain reaction.

discordant for age (14 years versus 24 years) when compared with the original corresponding admission and was excluded from the analysis. The remaining 15 met the criteria to be defined as readmissions as described in the methodology. Taking these 15 readmissions into account, the KCMC had a total of 434 admissions during the study period, of which 239 (55%) were male. The mean age of admissions was 29.9 years and 106 (24%) were aged 18 years or less.

All 15 readmissions had only one previous admission. One patient did not have an EVD PCR result upon the first admission, as this person left the centre before testing could be done. The 14 remaining readmissions were all related to a prior admission whereby the PCR result was negative for EVD. The distribution of readmissions among all admissions to the KCMC is presented on the epidemiological curve in Figure2. It shows that four readmissions occurred during the first half of the outbreak while the remaining 11 presented in the second half.

Of the 15 readmissions, seven were male and four were aged 18 years or less. The mean age of readmissions was 27.9 years (range: 1.75–48 years).

A positive EVD PCR test was obtained for nine readmissions of which five died, three were cured and one is a current inpatient at KCMC (Table 1). The crude readmission ratio (CRR) for KCMC was 11% (15/138) while the positive readmission ratio (PRR) was 7% (9/138). The average length of stay (LOS) at the KCMC for primary admissions linked to any readmission was 1.9 days (28/15) whereas the average LOS for primary admissions with corresponding EVD PCR positive and negative readmissions was 2 (18/9) and 1.7 (10/6) days respectively. Regarding the three readmissions who were cured, they had an average LOS after readmission of 22 days (66/3) while the five readmissions who died and six who were not a case had an average LOS of seven (35/5) and 2.3 (14/6) days respectively (Table 1).

The interval between discharge from primary admission and follow-up readmission to the KCMC for all readmissions was an average of 9.4 days with a range from four to 21 days (Table 2). Cases 1 to 15 also had a documented epidemiological contact with a suspected or confirmed case of Ebola (excluding their primary admission to the KCMC) within the prior 21 days to their readmission to the KCMC (Table 2). The majority (10/15) of these epidemiological contact types were household followed by occupational (3/15) and funeral (2/15) (Table 2).

Discussion

In response to the current EVD outbreak in West Africa, numerous Ebola CMCs are operating concurrently in the region [3]. MSF has previously set the standard for constructing and managing these centres in remote African settings [9,10]. The literature indicates that hospitals with inadequate infection control procedures have previously augmented filovirus outbreaks while appropriately run CMCs help contain them [4]. The emerging situation in Sierra Leone of patients who were initially discharged as non-cases from the KCMC and then returning as EVD PCR positive cases within 21 days has caused medical staff to question if CMCs are acting as potential amplifiers of infection during this outbreak even though appropriate infection control measures are being followed. Such a question is of public health importance to the overall future control of the outbreak.

This study has demonstrated that 7% of patients who were originally discharged as non-cases were readmitted as EVD PCR positive cases. Notably all readmissions occurred within 21 days of primary admission discharge, which is equivalent to the incubation period of EVD. This readmission's timeframe raises the possibility of nosocomial infection having occurred during the primary admission. The average LOS for primary admissions linked to positive readmissions was two days, during which time patients were admitted to the suspect and probable wards of the CMC. Infection control measures are strictly enforced in these wards, which are separated by barrier fencing from the confirmed wards in order to minimise the risk of nosocomial infection. Patients in the suspect/probable wards are encouraged to maintain a minimum distance from other patients at all times and not to touch or use items belonging to other patients. The number of cases per ward is capped to prevent overcrowding. Chlorine solution hand washing facilities are located at multiple points for patient and staff use. Patients can only be transferred from suspect/probable to confirmed wards and not vice versa to prevent spread of infection within the CMC. Hygienist staff regularly disinfects all areas within both the low and high risk zones. The implementation of strict infection control protocol in the suspect/probable wards and the wider CMC in general reduces but can never eliminate the hazard of nosocomial EVD infection.

Importantly, all readmissions to the KCMC had documented epidemiological contacts with suspected or confirmed Ebola cases within the previous 21 days that did not include the original admission to the KCMC. This is a relatively reassuring finding as it acts as a counter weight to the fact that all readmissions occurred within the incubation period of EVD. The source of infection for positive readmissions is as likely to be the household, funeral and occupational contacts documented, as the primary admission to the KCMC. Positive readmissions partly reflect the continuous intense transmission of the virus in the surrounding community.

It is notable that patients who were discharged as not a case had an average LOS of almost two days in the suspect or probable wards. Unfortunately, it was not possible to distinguish between suspect and probable admissions and readmissions, as this information was not sufficiently recorded on the case investigation

Table 2

Epidemiological contact information for readmissions to the Ebola case management centre, Kailahun, Sierra Leone, 26 June–1 September 2014 (n=15 readmissions)

Patient number	Interval (days) between primary admission discharge and readmission	Presence of an epidemiological contact explaining readmission (excluding primary admission to KCMC)	Type of epidemiological contact prior to readmission (excluding primary admission to KCMC)	Interval (days) between most recent epidemiological contact (excluding primary admission to KCMC) and symptom onset prior to readmission	Epidemiological contact information
1[a]	4	Yes	Household	6	Patient 1 lived with two family members who were both admitted to KCMC six days before patient 1 was readmitted to KCMC. The two family members (EVD positive) respectively died three and four days after their admission.
2[a]	6	Yes	Funeral	9	Patient 2 lived with respective spouse who died of suspected EVD 11 days before patient 2 was readmitted to KCMC. Patient 2 had touched the body during the funeral.
3	4	Yes	Household	5	Patient 3 lived with three persons and patient 4. The first of these three persons was admitted to KCMC eight days before patient 3 was readmitted to KCMC and the two others six days before. All were EVD positive, two died and one was cured. Patient 4 was admitted to KCMC the same day as patient three.
4[a]	4	Yes	Household	5	Patient 4 lived with three persons and patient 3. The first of these 3 persons was admitted to KCMC eight days before patient 4 was readmitted to KCMC and the two others six days before. All were EVD positive, two died and one was cured. Patient 3 was readmitted to KCMC the same day as patient 4 but never developed EVD.
5	21	Yes	Occupational	Continual exposure	Patient 5 worked for the Ministry of Health burial team, a high risk occupation for developing EVD.
6[a]	6	Yes	Funeral	9	Patient 6 lived with respective mother who died of suspected EVD 10 days before patient 6 was readmitted to KCMC. Patient 6 touched the body during the funeral.
7[a]	12	Yes	Household	12	Patient 7 lived with five extended family members who were all admitted (all EVD positive) to KCMC 15 days before this patient was readmitted to KCMC. All were cured subsequent to medical care.
8[a]	14	Yes	Household	2	Patient 8 lived with two family members. One was admitted to KCMC (EVD positive) 17 days before patient 8 was readmitted to KCMC and was subsequently discharged as cured five days later, the other was admitted to KCMC five days before patient 8 was readmitted to KCMC and then discharged as cured 23 days later.
9[a]	9	Yes	Household	10	Patient 9 lived with two family members. One was admitted (EVD positive) to KCMC 12 days before patient 9 was readmitted to KCMC and subsequently discharged as cured five days later. The other was admitted to KCMC five days after patient 9 was readmitted to the KCMC. This person died three days after being admitted.
10	12	Yes	Household	8	Patient 10 lived with five family members, who were admitted (all positive for EVD) to KCMC 14 days before patient 10 was first admitted to the KCMC. Three of the family members died and two were subsequently discharged as cured.
11[a]	14	Yes	Occupational	Continual exposure	Patient 11 worked as a nurse, a high risk occupation for developing EVD.
12[a]	5	Yes	Household	3	Patient 12 lived with a family member who was admitted to KCMC the same day than patient 12 was readmitted to KCMC and who died five days later.
13	9	Yes	Household	11	Patient 13 lived with a family member and two children. The two children were admitted to KCMC 16 days before patient 13 was readmitted to the KCMC. One child died four days later and the other was discharged as cured 16 days after admission.
14	16	Yes	Occupational	Continual exposure	Patient 14 worked as a laboratory technician, a high risk occupation for developing EVD.
15	5	Yes	Household	10	Patient 15 lived with respective spouse who was admitted to KCMC (EVD positive) 11 days before patient 15 was readmitted to KCMC. The spouse died four days after respective admission.

EVD: Ebola virus disease; KCMC: Kailahun Ebola case management centre.

[a] Patient who tested positive for EVD after readmission.

forms. Efforts are ongoing to collect this information in a more systematic manner in the field. There are multiple reasons for the LOS of almost two days including the lack of availability of a 24 hour laboratory service on-site to process blood samples and the restriction of the phlebotomy service to morning times only due to staff workload and safety concerns regarding performing venesection at night time. A proportion of newly admitted patients will require a repeat EVD PCR test if symptom duration has been less than 72 hours to rule out a false negative result [9]. In such cases the symptomatic patient will have to spend additional time in the suspect or probable ward until a repeat test is performed at the appropriate time. However, for newly arrived patients who already had a minimum of three days of symptoms, it is imperative that phlebotomy and laboratory analysis be performed as quickly as reasonably possible in order to prevent the risk of potential nosocomial EVD infection to patients who could be non-cases staying overnight in the suspect or probable wards. Ideally, phlebotomy and laboratory analysis at the CMC should be provided on a 24 hour basis where feasible. Furthermore, new bedside rapid diagnostic tests (RDT) for EVD that do not require phlebotomy are urgently needed. Such technology improves the timeliness of diagnosis for patients and reduces the risk of infections for healthcare staff.

The epidemiological curve showed that the majority of readmissions occurred during the second half of the outbreak to date. Readmissions can only develop from the pool of discharged non-cases because EVD positive cases have immunity to the specific strain if they survive to discharge [11,12]. On further inspection of the epidemiological curve it appears that positive readmissions have clustered following peaks in primary admissions. The clustering of three positive readmissions between 15 and 21 July and five positive readmissions between 10 and 19 August occurred within 21 days of the primary admissions peaks on 2 and 3 July and on 1 and 2 August respectively. The clustering of readmissions following primary admission peaks within the EVD incubation period suggests the possibility of the presence of superspreaders of the virus.

This study has shown the importance of analysing CMC readmissions to understand what exposures contribute to positive readmissions and to detect potential nosocomial EVD infection when no other sources of infection can be identified. For all positive readmissions described in this study an exposure, in addition to the primary admission, was identified within the EVD incubation period.

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Conflict of interest

None declared.

Author's contributions

Gabriel Fitzpatrick collected data in the MSF CMC in Sierra Leone and wrote the first draft of the paper and incorporated all co-authors comments into the final draft of the paper. Florian Vogt, Osman Bamba Moi Gbabai, Benjamin Black, Maud Santantonio, Elin Folkesson, Tom Decroo and Michel Van Herp all reviewed the paper and submitted their comments, which were included in the final draft of the paper.

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Transmission dynamics and control of Ebola virus disease outbreak in Nigeria, July to September 2014

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We analyse up-to-date epidemiological data of the Ebola virus disease outbreak in Nigeria as of 1 October 2014 in order to estimate the case fatality rate, the proportion of healthcare workers infected and the transmission tree. We also model the impact of control interventions on the size of the epidemic. Results indicate that Nigeria's quick and forceful implementation of control interventions was determinant in controlling the outbreak rapidly and avoiding a far worse scenario in this country.

Outbreak details

The largest Ebola virus disease (EVD) outbreak to date is ongoing in West Africa, particularly in Guinea, Sierra Leone and Liberia, with a total of 7,178 reported cases including 3,338 deaths as of 1 October 2014 [1]. A total of 20 EVD cases (19 laboratory confirmed, one probable) have been reported in Nigeria, with no new cases reported since 5 September 2014. All 20 cases stemmed from a single importation from a traveller returning from Liberia on 20 July 2014 [2]. The Nigerian index case had visited and cared for a sibling in Liberia who died from the disease on 8 July 2014 [2,3]. Despite being aware of his exposure to Ebolavirus in Liberia, the index case flew from Liberia to Lagos, Nigeria, on a commercial airplane on 20 July 2014, with a stopover in Lomé, Togo. The case became symptomatic while flying and collapsed at Lagos airport upon landing, which prompted him to seek medical attention and led to a number people being exposed to Ebolavirus. Epidemiological investigation revealed that the index case had contracted Ebolavirus in Liberia; the patient died on 25 July 2014 [4].

A total of 894 contacts were subsequently linked to this index case, including the primary, secondary and tertiary contacts [2].** Importantly, one of the primary contacts of the index case had travelled to Port Harcourt, the capital of Rivers State, at the end of July 2014 and was cared for by a healthcare professional who subsequently became infected and died on 22 August 2014. This deceased healthcare worker was in turn linked to a total of 526 contacts in Port Harcourt [2]. As of 1 October 2014, all contacts had completed the 21-day surveillance follow-up, including those under surveillance in Rivers State, with no new report of incident cases [2]. The World Health Organization is soon to officially declare Nigeria free of active Ebolavirus transmission [2].

Here we assess the epidemiological data for the EVD outbreak in Nigeria from 20 July to 1 October 2014, and use a dynamic disease transmission model to illustrate the effect of forceful interventions in rapidly containing the EVD outbreak in Nigeria. The interventions included timely implementation of careful contact tracing and effective isolation of infectious individuals.

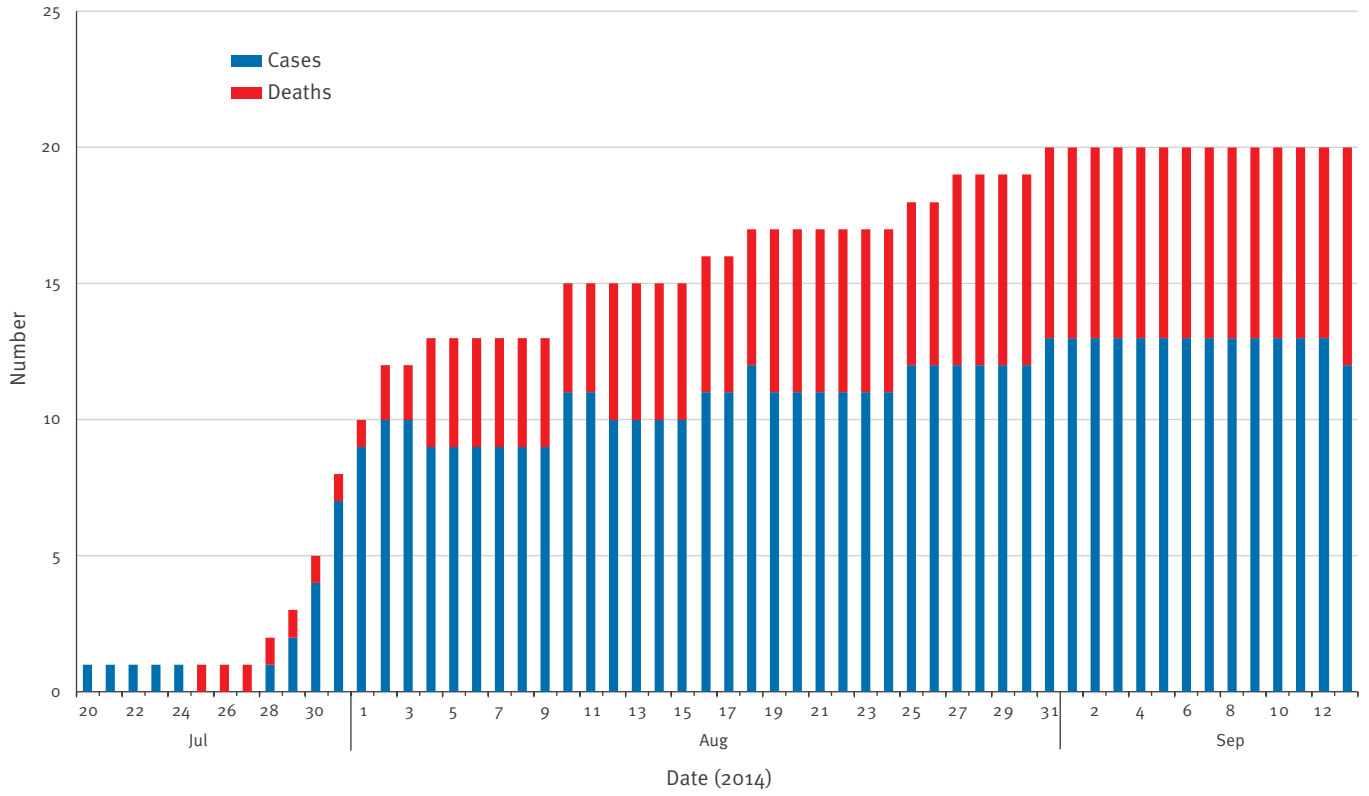
Data sources

We used up-to-date epidemiological data for the EVD outbreak in Nigeria available from public sources as of 1 October 2014 [1,5-32].

The 19 laboratory-confirmed cases were diagnosed by reverse transcription (RT)-PCR at Lagos University Teaching Hospital and Redeemer University in Lagos. Probable cases are suspected cases evaluated by a clinician or any deceased suspected case with an epidemiological link with a confirmed EVD case [1,2].

Figure 1

Cumulative reported cases and deaths of Ebola virus disease in Nigeria, July–September 2014*,***



A total of 19 laboratory-confirmed cases, one probable case and eight deaths among the cases have been reported as of 1 October 2014. The index case entered Nigeria on 20 July 2014 and the onset of outbreak is taken from that date.

To build the Ebola virus disease epidemic curve, we reviewed all relevant information published in *Morbidity and Mortality Weekly Report* [2] and World Health Organization Ebola situational reports and updates for Nigeria published during July to September 2014 [1,5-31] and categorised the 20 reported Ebola virus disease patients by reporting date and discharge status (dead/alive).

The diagnosis of the index case took approximately three days, while results of the tests for the other confirmed cases were typically available within 24 hours. Samples were also sent to the World Health Organization Reference Laboratory in Dakar, Senegal, for confirmation.

All symptomatic contacts were initially held in an isolation ward. Following laboratory confirmation of EVD, all positive symptomatic contacts were immediately moved to an EVD treatment centre. Asymptomatic suspected contacts were separated from symptomatic contacts. Negative asymptomatic individuals were discharged immediately [2].

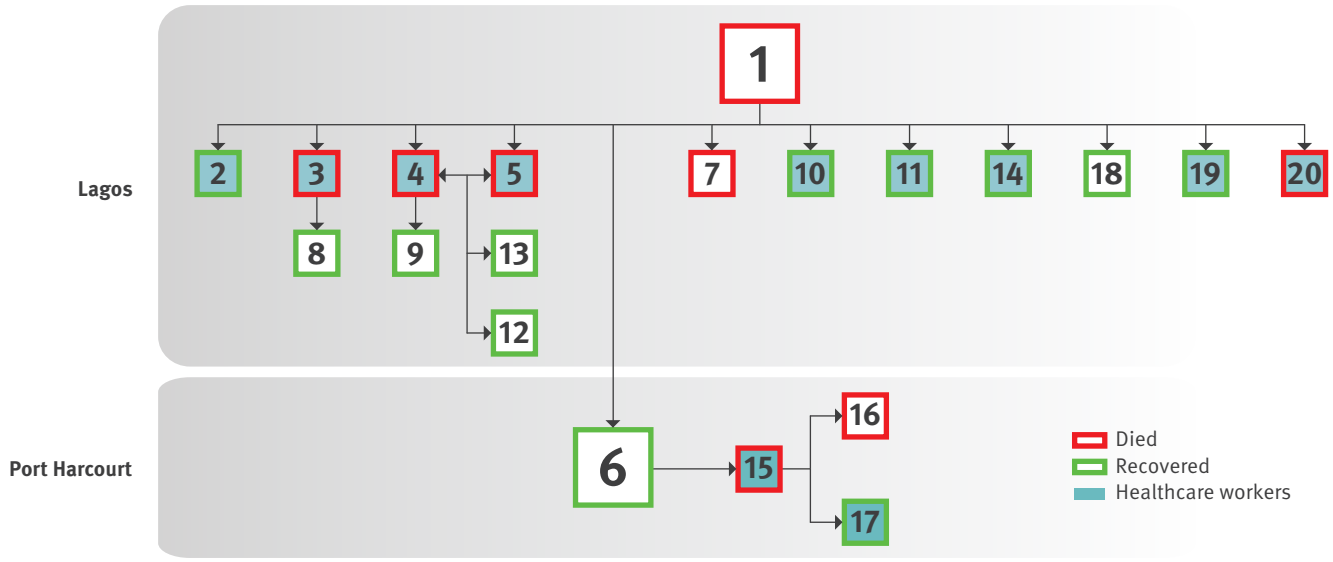
Modelling Ebolavirus transmission and control

We estimated the case fatality rate (number of reported deaths/number of reported cases), the proportion of infected healthcare workers, and the mean number of secondary cases by generation of the disease by analysing a transmission tree. We employed two compartments to differentiate between infectious individuals who were in the community and those who had been identified and placed in isolation in hospital. Using epidemic modelling, we also projected the size of the outbreak in Nigeria if control interventions had been implemented at different dates, and hence estimate how many cases were prevented by early start of interventions.

We carried out stochastic EVD outbreak simulations based on a simplified version of the model proposed by Legrand et al. [33], which was developed to classify the contribution of community, funeral and healthcare settings to the total force of infection. Although the model also accounts for transmission stemming from burial practices that involve touching the body of the deceased, this feature is believed to have less influence on transmission in the EVD outbreak in Nigeria [34]. For the sake of simplicity, we only classified transmission in the community and in healthcare settings by adjusting baseline transmission rates, diagnostic rates and enhancement of infection-control measures (e.g.

Figure 2

Transmission tree of the Ebola virus disease outbreak in Nigeria, July–September 2014 *,***



To develop a detailed transmission tree for the patients included in Figure 1, we built on a published tree [2], cross-referencing the information in the tree with that in World Health Organization reports [1,5-31], as well as information from local newspaper reports (e.g. [32]) that provided details on individual patient's infection links and their occupation. We categorised each patient according to the transmission setting (Ebolavirus acquired in a healthcare setting or the community), patient's geographical location (Lagos or Port Harcourt) and discharge status (dead/alive).

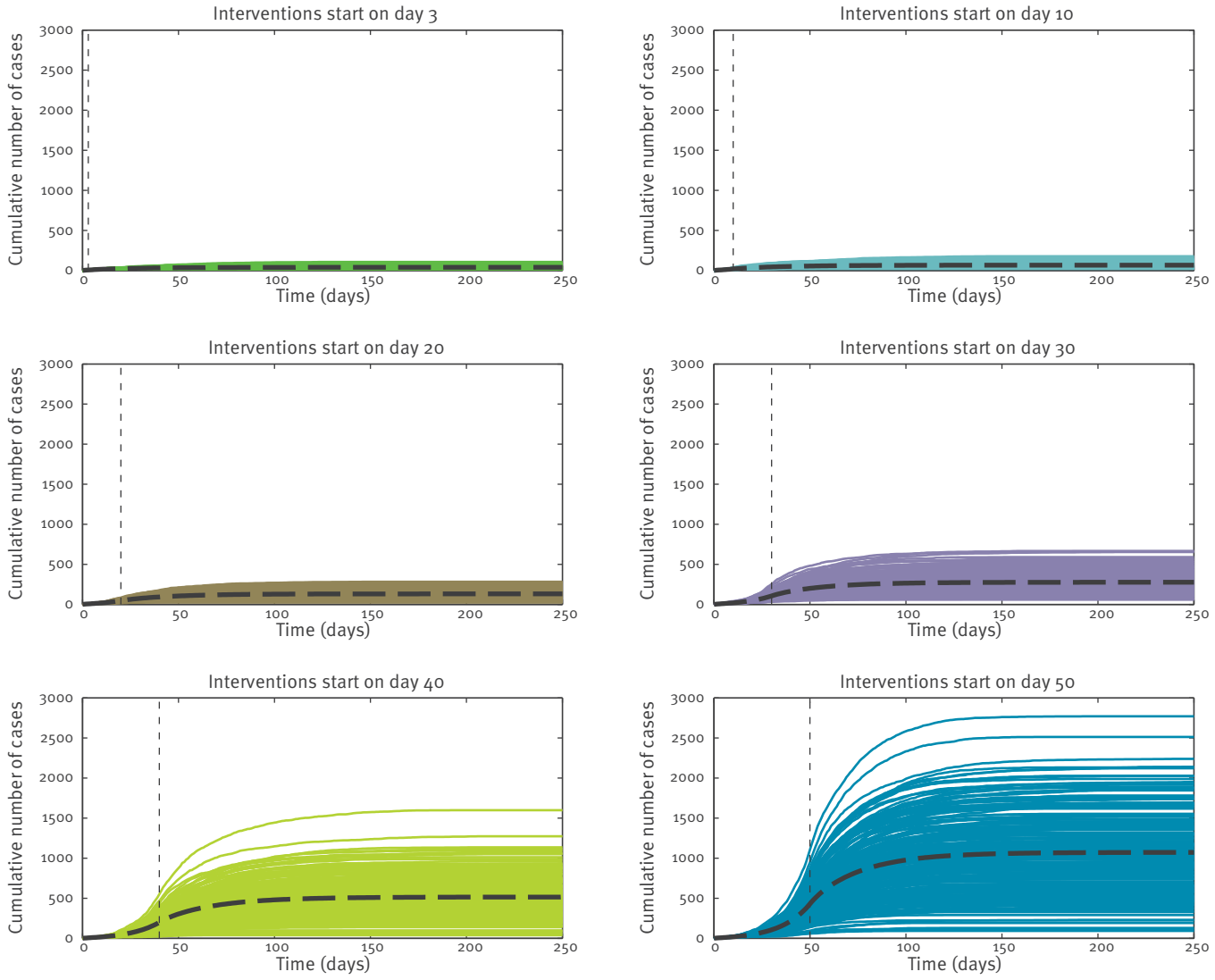
strict use of protective equipment by healthcare workers and effective isolation of infectious individuals).

The modelled population was divided into five categories: susceptible individuals (S); exposed individuals (E); Infectious and symptomatic individuals (I); hospitalised individuals (H); and individuals removed from isolation after recovery or disease-induced death (P). Susceptible individuals infected through contact with infectious individuals (secondary cases) enter the latent period at mean rate $\beta(t)\ (I + I(t)\ H)\ /N(t)$ where $\beta(t)$ is the mean human-to-human transmission rate per day, $I(t)$ quantifies the mean relative transmissibility of hospitalised patients compared with that in symptomatic patients in the community, and N(t) is the total population size at time t. Thus, values of this parameter between 0 and 1 measure the effectiveness of the isolation of infectious individuals that decrease Ebolavirus transmission probability below that seen in the community. Values close to 0 illustrate 'near-perfect' isolation, while values closer to 1 illustrate 'imperfect' isolation strategies. Symptomatic infectious individuals I are hospitalised at a time-dependent mean rate $\gamma_a(t)$ or else recover without being hospitalised, at the mean rate γ_I. Individuals in the 'removed' category do not contribute to the transmission process. For simplicity, it can be assumed that the time-dependent transmission rate $\beta(t)$, the mean relative transmissibility of hospitalised patients $I(t)$, and the mean diagnostic rate $\gamma_a(t)$, remain constant with values at β_0, I_0, and γ_{a0} before the implementation of intervention measures. Once control interventions are instituted at time τ, the transmission rate decreases to $\beta_1 (\beta_1 < \beta_0)$, the mean relative transmissibility of hospitalised patients decreases to I_1 $(I_1 < I_0)$ by enhancing infection control measures in healthcare settings, while the diagnostic rate increases to γ_{a1} $(\gamma_{a0} < \gamma_{a1})$ through contact tracing activities.

We carried out stochastic simulations of this transmission model to project the size of the outbreak in Nigeria if interventions (index case identification, contact tracing and isolation of those infected) had been started at different dates (range of 3 to 50 days after the index case arrived in Nigeria), and hence estimate how many cases were prevented by an early start of interventions. Baseline epidemiological parameters were set according to the epidemiology of EVD (i.e. incubation period of 6–12 days [35,36], infectious period of 5–7 days [37,38], case fatality rate: 35–50% [36]). Moreover, the mean time from symptom onset to diagnosis (γ_{a0}) was set at five days before the implementation of interventions [11]. Without loss of generality, we set the effective population size at 10,000,000 (assuming larger population sizes, for example, did not affect our conclusions). R_0 (the basic reproduction number) denotes the transmission potential before the start of interventions in a completely susceptible population [39], while we refer to R, the reproduction number, when transmission is affected by control interventions. We varied R_0 in the range 1.5–2.0 before the start of interventions, based on estimates from other affected countries [40-43]. R_0

Figure 3

Simulation results from calibrating the transmission model to assess the timing of control interventions on the size of the Ebola virus disease outbreak in Nigeria



I: mean relative transmissibility of hospitalised patients; R_0: basic reproduction number.

Baseline epidemiological parameters were set according to the epidemiology of Ebola virus disease and R_0=2 before the start of interventions. Moreover, the mean time from symptom onset to diagnosis ($1/\gamma_{a0}$) was set at five days before the implementation of interventions, and the effective population size was set at 10,000,000. After the start of interventions, the mean time from onset to diagnosis was reduced from five days to one day, and the relative infectiousness of hospitalised individuals was reduced by 80% (i.e. I_0=1, I_1=0.2) to reflect the strict enhancement in infection control measures in hospital settings. Day 0 corresponds to the day when the index case was introduced in the population. We analysed 200 stochastic model simulations.

was set by adjusting the baseline transmission rate. After the start of the interventions, only two parameters were adjusted: (i) the mean time from symptom onset to diagnosis was reduced from five days to one day; and (ii) the infectiousness of hospitalised individuals was reduced by 80% to reflect the tightening of infection control measures in hospital settings relative to levels before the identification of the index case (i.e. I_0 =1, I_1 = 0.2).

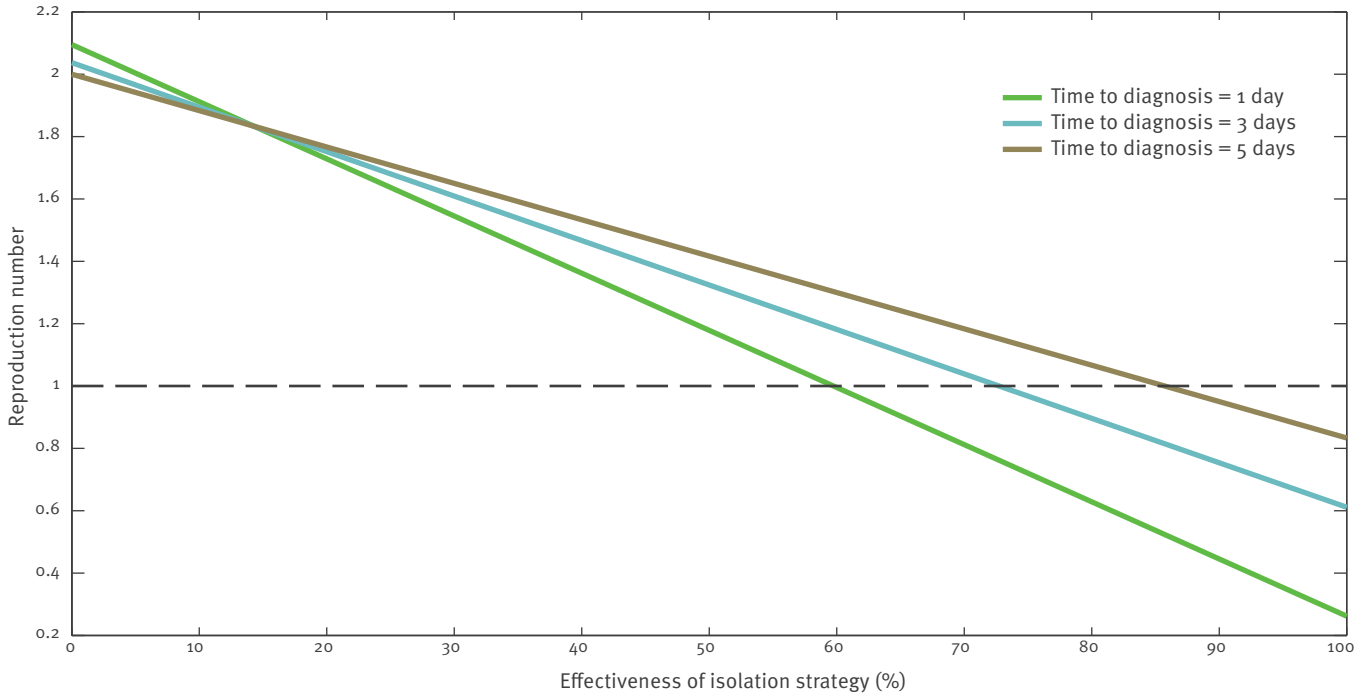
We ran 200 stochastic simulations starting with the introduction of an index case and 12 local individuals exposed by the index case at the start of the outbreak (i.e. $I(0)$=1, $E(0)$=12). We set the timing of start of interventions τ at day 3 of the simulated outbreak (in line with the Nigerian outbreak response), as well as 10, 20, 30, 40 and 50 days, and compared the predicted final epidemic size with that of the outbreak in Nigeria (i.e. 20 EVD cases (laboratory-confirmed and probable)). Simulation code in Matlab is available upon request from the authors.

Results

Eight of the 20 reported EVD cases reported in Nigeria have died, giving an estimated case fatality rate of 40% (95% CI: 22–61) (Figure 1). Of the 20 cases, 11

Figure 4

Effects of the effectiveness of isolation of infectious individuals on the reproduction number for three values of the diagnostic rate, Ebola virus disease outbreak, Nigeria



I: mean relative transmissibility of hospitalised patients; R: reproduction number.

There is a critical level of isolation effectiveness of infectious individuals estimated at about 60% with a mean time from symptoms onset to diagnosis of one day, which is necessary to reduce the reproduction number below the epidemic threshold at R=1.0 and halt the spread of Ebola virus disease.

The baseline R_0 was set at 2.0 with I_0 =1 and the mean time from symptom onset to diagnosis ($1/\gamma_{a0}$) was five days before the implementation of interventions.

were healthcare workers; nine of whom acquired the virus from the index case before the disease was identified in the country [1].

We built the transmission tree of the EVD outbreak, which provides information on the history of each case (Figure 2). The index case generated 12 secondary cases in the first generation of the disease. Five secondary cases were generated in the second generation and two secondary cases in the third generation. This leads to a rough empirical estimate of the reproduction number according to disease generation decreasing from 12 during the first generation, to approximately 0.4 during the second and third disease generations.

The projected effect of control interventions on the transmission of Ebolavirus in Nigeria is illustrated in Figure 3.

The effect of the effectiveness of isolation of infectious individuals on the reproduction number is shown in Figure 4 for three values of the diagnostic rate. There is a critical level of isolation effectiveness of infectious individuals estimated at about 60% with a mean time from symptom onset to diagnosis of one day, which is necessary to reduce the reproduction number below the epidemic threshold at R=1.0 and halt the spread of EVD (Figure 4).

Discussion

We have analysed epidemiological data of what appears to be a limited outbreak of EVD in Nigeria based on data available as of 1 October 2014, with no new EVD cases reported since 5 September 2014. The swift control of the outbreak was likely facilitated by the early detection of the index entering Nigeria from a country where disease is widespread, in combination with intense contact tracing efforts of all contacts of this index case and the subsequent isolation of infected secondary cases [2]. In contrast, the initial outbreak in Guinea remained undetected for several weeks [44]. This detection delay facilitated the transnational spread of the virus to Sierra Leone and Liberia, while difficulties and at times inability to track and contain infectious individuals compounded the situation and resulted in an as yet uncontrolled epidemic in these countries.

We estimated a mean case fatality rate of 40% (95% CI: 22–61) for the EVD outbreak in Nigeria. This estimate based on a small sample size is at the lower end of estimates from previous outbreaks, ranging from 41% to 89% [33] and is likely a result of supportive care

offered in dedicated facilities put in place in a timely fashion by the Nigerian authorities. In comparison, the EVD case fatality rate in the ongoing outbreak in Guinea, Sierra Leone and Liberia has been estimated at 70% (range: 61– 89) [36]. As is the case for any emerging infection, these estimates have to be considered with caution as they are prone to many biases, including under-reporting of milder symptomatic cases (affecting the denominator) and censoring effects related to the unknown final outcome of the most recent infections.

The toll on healthcare workers in the EVD outbreak has been substantial, as they account for 11 of the 20 EVD cases in Nigeria. Past EVD outbreaks have been amplified in healthcare settings, e.g. [45,46], including in the ongoing epidemic in West Africa, with about 5% of the total number of reported EVD cases being healthcare workers based on data available as of 1 October 2014 [20,47].

Fortunately, past experience with the Zaire Ebolavirus strain also indicates that early, intense and sustained infection control measures in healthcare settings can substantially reduce the size and geographical scope of EVD outbreaks [48], which is consistent with the recent Nigerian experience.

The number of secondary cases decreased over subsequent disease generations in Nigeria, reflecting the effects of interventions, in particular the intense and rapid contact tracing strategy, the continuous surveillance of potential contacts, and the largely effective isolation of infectious individuals. Indeed, the mean reproduction number among secondary cases in Nigeria (i.e. excluding the contribution from the imported traveller) was 0.4 in the presence of control interventions. This number is below the epidemic threshold for disease spread, while a recent estimate of R derived from the growth rate pattern for Nigeria straddled the epidemic threshold of 1.0 [36]. In contrast, recent estimates of the reproduction number for the ongoing EVD epidemic in Sierra Leone and Liberia range between 1.5 and 2 [40-43], indicating that the outbreak is yet to be brought under control [43]. Moreover, the size of the outbreak in Nigeria is in agreement with our model simulation results when we assume that interventions were quickly instituted on day 3 of the outbreak. Our model simulations of delayed interventions, in accordance with large outbreaks in the broader West African region, demonstrate the necessity of rapid and forceful control measures. The Nigerian experience offers a critically important lesson to countries in the region not yet affected by the EVD epidemic, as well as to countries in other regions of the world that risk importation of EVD and that must remain vigilant. As a case in point, the recent importation of an EVD case in the United States from Liberia [49] proves that no country is immune to the risk of EVD in a globally connected world, but that rapid case identification and forceful interventions can stop transmission.

* Addendum

To build the EVD epidemic curve (Figure 1), we reviewed all relevant information published in Morbidity and Mortality Weekly Report *[2] and WHO Ebola situational reports and updates for Nigeria published during July to September 2014 [1,5-31] and categorised the 20 reported EVD patients by reporting date and discharge status (dead/alive). To develop a detailed transmission tree for these patients (Figure 2), we built on a published tree [2], cross-referencing the information in the tree with that in the WHO reports, as well as information from local newspaper reports (e.g. [32]) that provided details on individual patient's infection links and their occupation. We categorised each patient according to the transmission setting (Ebolavirus acquired in a healthcare setting or the community), patient's geographical location (Lagos or Port Harcourt) and discharge status (dead/alive). The addendum was added on 30 April 2015, at the request of the authors, following comments from colleagues involved in the outbreak response in Nigeria.*

** Authors' correction

The following corrections were made on 30 April 2015 at the request of the authors, following comments from colleagues involved in the outbreak response in Nigeria and facilitated by the editors of Eurosurveillance: the number of contacts investigated through contact tracing was changed from 898 to 894 and unnecessary information regarding contact type was removed; individual-level patient information provided in Figure 2 was removed, as was a sentence in the text providing details of a nurse who cared for the index patient, for confidentiality purposes. The reference list was expanded to include additional supporting documents and the citations were amended accordingly throughout the article. Finally, a sentence pertaining to the management of contacts that tested negative for Ebolavirus was removed in response to comments from colleagues involved in the outbreak response in Nigeria. These changes do not have any bearing on the results or conclusions of the study.

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and grant number 1318788. III: Small: Data Management for Real-Time Data Driven Epidemic simulation.

Conflict of interest

None declared.

Authors' contributions

FOF, AS, DL and OT gathered data; FOF and GC-P conducted statistical analyses and modelling; FOF, GC-P, CV, LS, OT critique the manuscript. All authors contributed to the drafting and approval of the manuscript for submission.

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Epidemiology of pertussis in Italy: Disease trends over the last century

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We reviewed the epidemiology of pertussis in Italy over the last 125 years to identify disease trends and factors that could have influenced these trends. We described mortality rates (1888–2012), case fatality rates (1925–2012), cumulative incidence rates (1925–2013) and age-specific incidence rates (1974–2013). We compared data from routine surveillance with data from a paediatric sentinel surveillance system to estimate under-notification. Pertussis mortality decreased from 42.5 per 100,000 population in 1890 to no reported pertussis-related death after 2002. Incidence decreased from 86.3 per 100,000 in 1927 to 1 per 100,000 after 2008. Vaccine coverage increased from 32.8% in 1993 to about 96% after 2006. As for under-notification, mean sentinel/routine surveillance incidence ratio increased with age (from 1.8 in <1 year-olds to 12.9 in 10–14 year-olds). Pertussis mortality decreased before the introduction of immunisation. Incidence has decreased only after the introduction of pertussis vaccine and in particular after the achievement of a high immunisation coverage with acellular vaccines. Routine surveillance does not show an increase in cumulative incidence nor in ≥15 year-olds as reported by other countries. Underrecognition because of atypical presentation and the infrequent use of laboratory tests may be responsible for under-notification, and therefore affect incidence reports and management of immunisation programmes.

Introduction

Every year *Bordetella pertussis* infection causes nearly 16 million cases and 195,000 deaths in children worldwide [1]. Although an estimated 95% of pertussis cases is observed in developing countries, pertussis is a cause of concern in several developed countries, where the disease seems to be resurging despite a high vaccination coverage [2-4]. Recently, large outbreaks of pertussis have been observed in Europe, the United States and Australia [5-7]. A precise estimate of the burden of pertussis is far from being possible due to the interaction of underrecognition, underreporting, and lack of availability of diagnostic facilities [8].

Several authors have reviewed the epidemiology of pertussis over a long period of time to describe the disease trends and to investigate the role of factors that may affect these trends [4,9-11]. These studies have focused on the epidemiology of pertussis since the introduction of the immunisation in the mid-1940s and have investigated factors potentially involved in the resurgence of pertussis, including increased awareness, diagnosis and reporting, changes in vaccine composition or schedule, waning immunity, and evolution of the bacteria.

In Italy, recommendations for pertussis immunisation were released in 1961, when whole cell vaccines became available [12]. Nevertheless, vaccination coverage increased substantially only after the introduction of acellular pertussis vaccines in 1995 and, even further, after 2002, when the vaccine started to be offered free of charge by all Italian regions [13]. Based on routine surveillance data, Italy is currently a low incidence country and outbreaks or incidence peaks have been rarely reported after the achievement of a high immunisation coverage [14].

We reviewed the epidemiology of pertussis in Italy in the last 125 years to explore factors that affected its trend and to estimate the effect of the immunisation on the disease burden.

Methods

Data sources

Data on notified pertussis cases were obtained from the Ministry of Health, which collects notifications from the Surveillance System for Infectious Diseases in Italy [14]. The Italian Surveillance system is passive, universal, and mandatory. Notification of infectious diseases relies on physicians and has been regulated by law with acts issued since 1901. For pertussis the only criterion for notification was a clinical diagnosis based on the opinion of the physician examining the patient, until the introduction of the World Health Organization (WHO) case definition in 1999 that

better defined diagnostic criteria [13,15]. Although the European Union case definition of the year 2008 has been approved at European level [16], pertussis notification in Italy continues to rely mainly on a clinical case definition, and laboratory confirmation is not routinely adopted, despite the availability at national level of real time-PCR and serology [17]. Until 1974, surveillance reports included the total number of notified pertussis cases only; after 1974, reported cases were available by age group.

Data on pertussis mortality and on the Italian population demographics for the period 1862–2009 were obtained from the National Institute of Statistics [18].

We also analysed data on pertussis incidence from a sentinel surveillance system for vaccine preventable diseases in children aged 0–14 years [19,20]. This sentinel surveillance system was in place in Italy between 2000 and 2009, with about 11% of all Italian primary care paediatricians participating; the range of participation among the Italian regions was between 7 and 16% [20].
Data on pertussis vaccine coverage in the first 24 months of life were obtained from the Ministry of Health and from surveys on vaccine coverage [21-24].

Data analysis

We described pertussis epidemiology in Italy in four time windows. Period 1: 1888 to 1945, covering the late 19th century and nearly first half of the 20th century, including the two World Wars; period 2: 1946 to 1960, covering the pre-vaccine era after the second World War; period 3: 1961 to 1994, covering the time when whole cell vaccine became available and coverage was low (‹33%); and period 4: 1995 to 2012, covering the time when acellular vaccine was used and the coverage high (›87%).

We calculated mortality rates per 100,000 population for pertussis in Italy from 1888 to 2012, case fatality rates from 1925 to 2012, and incidence rates per 100,000 population for the entire Italian population from 1925 to 2013. We also calculated the age specific incidence rates from 1974 to 2013 for the following age groups: ‹1 year-olds, 1–4 years-old, 5–9 years-old, 10–14 years-old, ≥15 years-old.

Incidence rates by age group (‹1 year-olds, 1–4 years-old, 5–9 years-old, 10–14 years-old) from the paediatric sentinel surveillance system were used for comparison with routine surveillance data. Assuming a higher sensitivity of the sentinel surveillance system we calculated the average ratio between sentinel surveillance and routine notification rates by age group to estimate under-notification.

Since the sentinel surveillance system reported monthly notification data, we also investigated seasonality. We used one-way Analysis Of Variance (ANOVA) test to compare the period means and F-test to assess if differences between means were statistically significant. Moreover, in order to improve the identification of a seasonal pattern, we used spectral analysis. We examined the cyclical structure of the detrended time series in the frequency domain using the periodogram, which represents an estimate of the spectral density computed using the fast Fourier Transform (FFT). By applying the Hodrick-Prescott filter (with λ=14,400) to the monthly time series of pertussis incidence, we removed the trend component and used the detrended data to build a periodogram through the FFT, allowing to switch from the time function to the frequency domain function. We built up a periodogram with the scales frequency on the x-axis and the spectral density on the y-axis. Indicating with T the period and with N the number of observations, the scaled frequency was calculated as $f = N/T$, and denoting by ω the angular frequency, the scaled frequency was $f = \omega *(N/2\pi)$, where $\omega = 2\pi/T$.

Stata 11 and Gretl 1.9.14 were used for data analysis.

Results

Demographic changes

During the last century in Italy birth and mortality rates have progressively declined, whereas life expectancy has increased. Live births decreased from 37.5 per 1,000 inhabitants in 1862 to 9.5 in 2009. This corresponds to a reduction by nearly half from 1,119,563 alive newborns in 1888 to 566,125 in 2009, with a more marked decline during the World Wars and since the 1970s. Mortality rates for all causes decreased from 27.4 per 1,000 inhabitants in 1888 to 9.8 in 2009. The Italian population has continuously grown from 26 million in 1862 to 60 million in 2009, with a progressive aging of the population. The aging index, i.e. the ratio between adults aged ≥65 years and children aged ≤14 years, has increased from 15.9% in 1888 to 143.4% in 2009.

Descriptive Analysis

Period 1 (1888 to 1945)

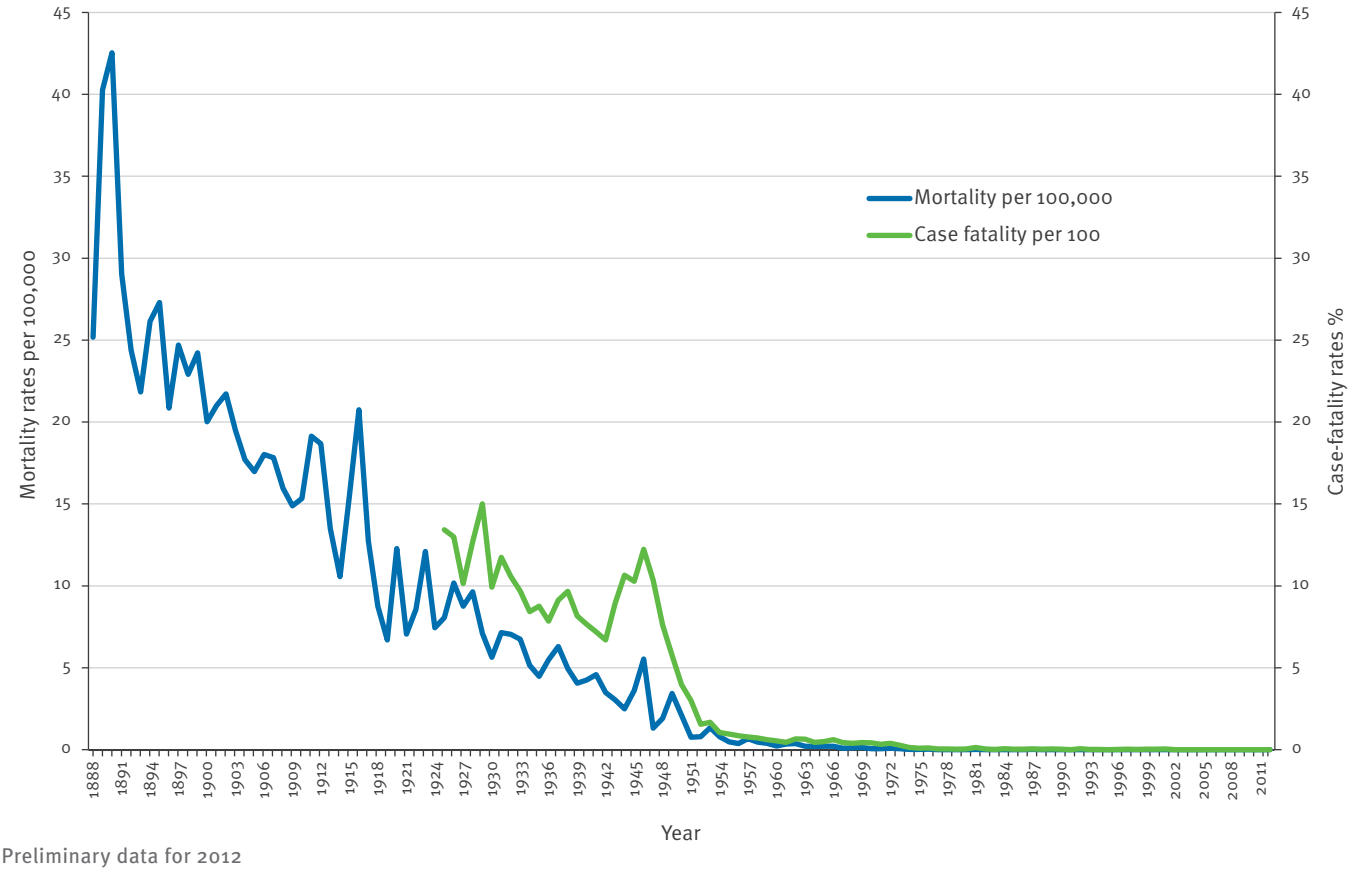
Pertussis mortality progressively decreased from 42.5 per 100,000 population in 1890 to 3.6 in 1945 (Figure 1). Case fatality rate decreased from 13.4% in 1925 to 6.7% in 1942, thereafter it increased again during the last two years of the second World War to 10.7% in 1944 and 10.3% in 1945 respectively (Figure 1). Pertussis incidence was high between 1925 and 1941, ranging between 50 and 70 per 100,000 population, with a peak of 86.3 in 1927 (Figure 2). The lowest incidence of pertussis was reported in 1944 (23.3/100,000). Epidemic cycles occurred regularly every three to five years.

Period 2 (1946 to 1960, pre-vaccine era)

Between 1946 and 1960, pertussis mortality and case fatality rates continued to decrease and reached very low numbers (Figure 1). Mortality decreased from 5.5 per 100,000 population in 1946 to 0.2 in 1960, and

Figure 1

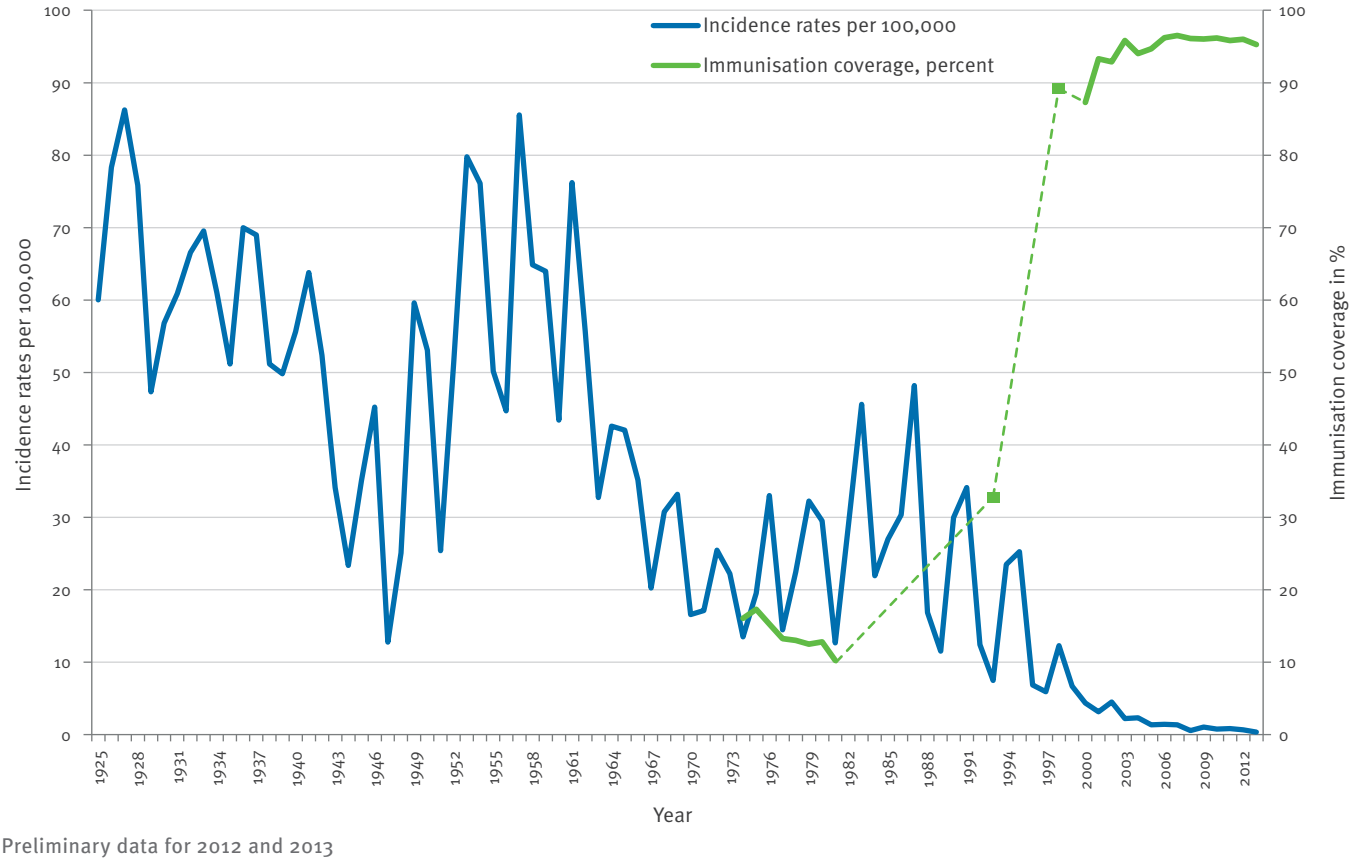
Pertussis mortality and case fatality, Italy, 1888–2012 and 1925–2012 respectively



Preliminary data for 2012

Figure 2

Pertussis incidence and pertussis immunisation coverage at 24 months, Italy, 1925–2013



Preliminary data for 2012 and 2013

case fatality rate from 12.2% to 0.5%. Pertussis deaths decreased from over 2,000 to around 100 per year. At the same time, a high and increasing incidence of pertussis was observed (Figure 2). Pertussis epidemic cycles continued to occur every three to five years with increasing incidence peaks (59.6/100,000 in 1949, 79.8/100,000 in 1953). The highest value (85.6/100,000) was observed in 1957.

Period 3 (1961 to 1994, whole cell vaccine, low coverage)

In 1961, recommendations for pertussis immunisation with the whole cell vaccine were released in Italy. Vaccination was not mandatory and immunisation policies differed among regions, with only some regions offering the immunisation for free [12]. Hereafter, pertussis mortality decreased further from 0.34 per 100,000 population in 1961 to 0.00 in 1994 (Figure 1). Mortality decreased from over 100 pertussis-related deaths per year between 1961 and 1966, to two pertussis-related deaths in 1994. The case fatality rate was below 1% during the whole period, with values between 0.1 and 0.0% after 1982 (Figure 1).

With the introduction of the whole cell vaccine, pertussis incidence showed a decreasing trend from 76.2 per 100,000 population in 1961 to 12.7 in 1981, although immunisation coverage was very low, with reported figures ranging between 10 and 16% during the years 1974 to 1981 (Figure 2). Epidemic cycles continued to occur every three to five years. An incidence peak was observed in the period 1983 to 1987, reaching values of 45.6 per 100,000 population in 1983 and 48.2 in 1987. Afterwards, incidence decreased again and the lowest value was reached in 1993 (7.5/100,000), when a vaccine coverage of 32.8% was reached. From 1974 to 1994 pertussis incidence was highest in children <1 year of age (range: 108.7–618.6/100,000 population) and in 1–4 years-old (range: 93.6–639.9/100,000) (Figure 3). Incidence in 5–9 year-old children was intermediate (range: 40.5–294.2/100,000 population), whereas pertussis incidence was lowest in adolescents (range: 1.2–34.4/100,000 population) and adults (range: 0.4–3.4/100,000).

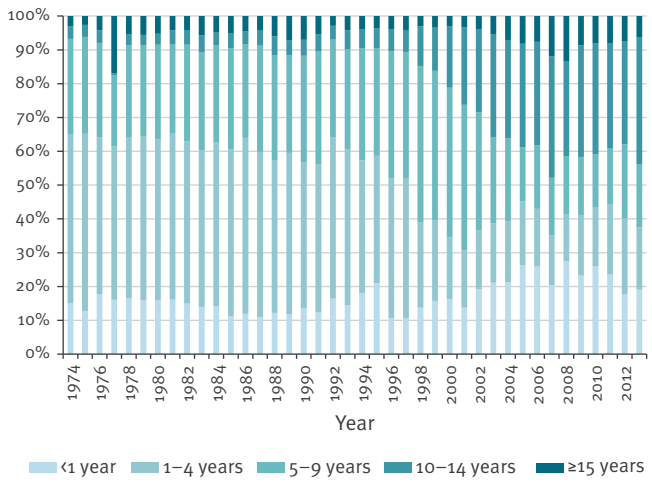
Period 4 (1995 to 2013, acellular vaccine, high coverage)

In 1995, acellular pertussis vaccines replaced whole cell vaccines with a recommended two-dose primary series and a booster at the age of 11 months. An additional preschool booster was recommended in 1999, and a booster in adolescents introduced in the childhood immunisation programme in 2012 [25]. Vaccine coverage increased dramatically, with an uptake of 89.2% in 1998, 87.3% in 2000, 94.7% in 2005, and 96.2% in 2010 (Figure 2). From 1995 to 2001, only one pertussis death per year was reported. No deaths have been reported since 2002.

After the introduction of the acellular pertussis vaccine, incidence peak values have decreased from 25.3 per 100,000 population in 1995 to 12.3 in 1998 (Figure 2). Since 1999, incidence has been below seven. Rates decreased below three per 100,000 population after the vaccine was offered free of charge in all Italian regions in 2002 and to around one per 100,000 population since 2008. Since 2002, epidemic cycles have been less clearly identifiable, due to the low incidence of pertussis. After the introduction of the acellular vaccines, incidence decreased in all age groups (Figure 3). Children <1 year of age continued to be the age group with the highest incidence rates (range: 6.9–556.4/100,000 population). Between 1998 and 2004, incidence rates were higher among children aged 5–9 years (range: 12.1–116.4/100,000 population) than in children aged 1–4 years (range: 10.5–81.8/100,000). Since 2003, incidence rates in 10–14 year-olds (range: 2.5–13.6/100,000 population) exceed rates in 1–4 (range: 1.6–11.2/100,000) and 5–9 years-old children (range: 1.3–12.4/100,000). The ≥15 years-old population, remains the age group with the lowest incidence rates (range: 0.0–1.1/100,000 population). After the introduction of the acellular vaccines, proportional distribution of reported cases by age group has changed (Figure 3). The proportion of reported cases in 1–4 and 5–9 year-olds has decreased, whereas the proportion of reported cases in those <1 year of age and 10–14 years-old has increased. Only a slight increase in the proportion of reported cases in the group ≥15 years of age has been observed.

Figure 3

Age percent distribution of pertussis cases, Italy, 1974–2013



Preliminary data for 2012 and 2013

Seasonality

Monthly data from the paediatric sentinel surveillance system from 2000 to 2009 showed a significant seasonal difference in incidence. The lowest incidence was reported in the fourth quarter, with a mean of 5.9 per 100,000 population, whereas values between 10 and 12.7 were observed during the other quarters (p-value=0.0027). The periodogram shows a peak for f=10 (corresponding to a periodicity of 11.8 months), with a spectral density of 61.04 and ω=0.53 (Figure 4).

An additional peak of lower amplitude (spectral density=22.44) is shown for f=5 (corresponding to a periodicity of 23.60 months). The strong annual periodicity in the Italian pertussis incidence peaked between March and August (spring/summer), while the minimum incidence was observed between September and February (autumn/winter). The annual and the biannual components of the time series stand for a sustained circulation of the disease in the period included in the analysis.

Under-notification

Data from the paediatric sentinel surveillance system in the period 2001 to 2008 showed significantly higher incidence rates than the routine surveillance, ranging from 13 to 360 per 100,000 population depending on the age group (Figure 5). Incidence rates showed a decreasing trend in all age groups. The age group with the highest incidence rates was 10–14 year-olds. Since 2005, incidence rates in 1–4 year-olds have exceeded incidence in children <1 year of age and those 5–9 years-old. Under-notification was lowest in children <1 year of age, with a mean sentinel/routine surveillance ratio of 1.8 in this age group. Under-notification increased in older age groups, with a mean ratio of 11.8 in 1–4 years-old children, 9.2 in 5–9 year-olds, and 12.9 in 10–14 year-olds.

Discussion

The epidemiology of pertussis has dramatically changed in Italy over the last century. Pertussis mortality has greatly declined, with no reported pertussis-related deaths since 2002. Pertussis incidence has decreased after the introduction of immunisation, in particular after achieving a high immunisation coverage with acellular vaccines after the year 2000. No resurgence of pertussis has been detected by routine surveillance data as of yet.

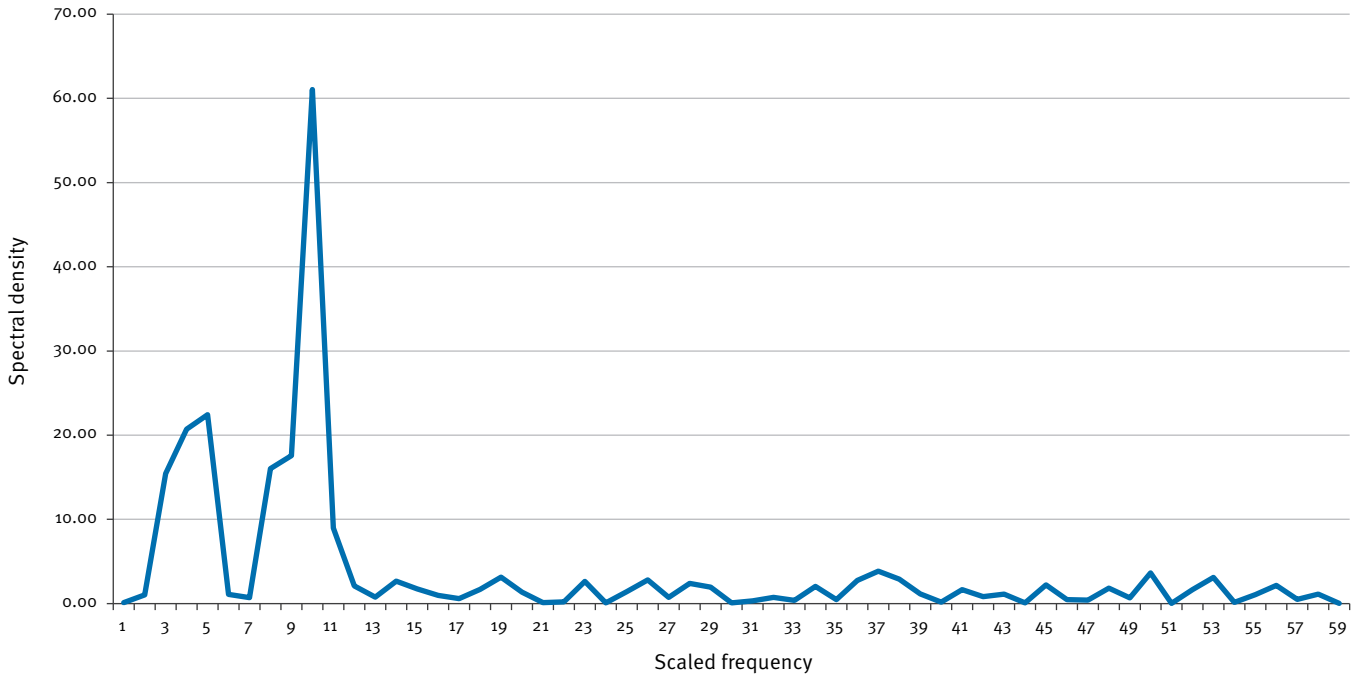
The improved living conditions of the Italian population and the achievement of better healthcare after the two World Wars likely affected pertussis mortality. Mortality and case fatality rates decreased indeed dramatically to values below 1 per 100,000 population and below 1% respectively, before the introduction of pertussis immunisation in the 1960s.

Figure 5

Pertussis incidence in children 0–14 years-old, Italian paediatric sentinel surveillance system , 2001–2008

Figure 4

Periodogram of pertussis incidence in children 0–14 years-old, Italian paediatric sentinel surveillance system, January 2000–October 2009



The introduction of pertussis immunisation has markedly influenced the incidence of the disease. Pertussis incidence started decreasing after the introduction of the whole cell vaccine in 1961, even if vaccine coverage was low. The most evident decrease in pertussis incidence has been observed after 1995, when the acellular pertussis vaccine was introduced, allowing to reach values ‹5 per 100,000 population after the year 2000. Since 2002, the vaccine has been offered free of charge to children ‹1 year of age by all Italian regions, allowing to achieve an immunisation coverage of about 96% after 2006.

The introduction of acellular vaccines and the progressive increase in vaccine coverage have also influenced the age distribution of the disease over the last two decades. During the low-coverage period, the highest pertussis incidence was in children ‹1 year and in those 1–4 years of age. After 1995, the highest incidence rates persisted in children ‹1 year of age, while incidence in 1–4 year-olds, the ones more protected by the infant immunisation, started decreasing. After an initial increase, incidence in children 5–9 years-old has been decreasing since 2003, following the introduction of the preschool booster in 1999. The constant increase of pertussis incidence in 10–14 years-old children can be explained by waning immunity [26-30], or by an increase in awareness of pertussis in this age group [11].

The introduction of immunisation programmes decreases the accumulation of susceptible individuals and therefore delays the occurrence of epidemic cycles [31]. In the case of pertussis in Italy, we observed that regular epidemic cycles persisted despite the demographic changes and even after the introduction of the immunisation. Only once a high immunisation coverage of ›94% was reached after 2002, epidemic cycles became unapparent. Immunity starts to wane between four to 10 years after pertussis immunisation, or even earlier according to recent reports [28-30], and also the protection after the natural disease is not lifelong [26,27]. Therefore, susceptible individuals are likely to have accumulated over time, especially in older age groups. Nevertheless, according to data from the routine surveillance system, Italy is not experiencing a resurgence of pertussis as reported in other developed countries [2-7]. In these countries a resurgence started to be observed several years after reaching high vaccine uptake rates [4,32]. Considering that in Italy a high immunisation coverage has been reached only after the year 2002, a resurgence of pertussis may be seen only in the years to come.

Data from the routine surveillance system do not show an increase in pertussis incidence in the ≥ 15 years-old population in Italy, as described in other European countries [2]. This is in contrast with a recent Italian seroepidemiological study, which suggests that *B. pertussis* actually circulates among adolescents and adults [33]. Underrecognition and missed diagnosis may partially explain the very low incidence rates reported in this age group in Italy. Symptoms of pertussis in adolescents, adults and previously vaccinated individuals are not always as typical as in younger children [34,35]. Indeed, a recent study showed that Italian physicians seldom suspect pertussis, and therefore do not request a laboratory confirmation test in older patients with a chronic cough [36]. The scarce use of laboratory confirmation of a suspected *B. pertussis* infection obviously reduces the possibility of diagnosis in patients with atypical pertussis presentation in all age groups.

Under-notification may also affect surveillance reports. Our results show a high under-notification ratio when comparing incidence figures from a sentinel surveillance system with routine reports. Moreover, under-notification ratios increased with age. Similar results have been recently reported from Poland [37]. Assuming that incidence figures based on surveillance reports should be adjusted for underrecognition and under-notification, the real incidence of pertussis may be much higher compared to figures reported through routine surveillance, with a higher difference in older age groups.

While in other countries changes in diagnostic criteria and techniques may have affected the reported pertussis incidence, notification in Italy still mainly relies on a clinical diagnosis, although laboratory diagnosis of *B. pertussis* infection is available [17]. This is obviously a limitation for the reliability of the surveillance system, but allows comparison of data over a very long time period.

In conclusion, before immunisation was available, pertussis incidence had not been influenced by historical or demographic changes in Italy, whereas mortality due to pertussis had already dramatically decreased. An evident decrease in pertussis incidence in Italy occurred after the introduction of immunisation and in particular after the achievement of a high vaccine coverage with the acellular vaccine. However, a decreased awareness of the disease, with underrecognition and under-notification, may play a role that has to be taken into account for the development, implementation and evaluation of immunisation programmes. Management of immunisation programmes strongly relies on surveillance data. Quality and sensitivity of surveillance should constantly be monitored and reviewed to adjust reported incidence rates. Since based on experiences elsewhere, a pertussis resurgence may occur in Italy, physicians should be educated to take into account a diagnosis of pertussis in individuals with atypical presentation and in older age groups. Moreover, the use of available laboratory confirmation methods, especially PCR, should be strongly supported in order to improve surveillance. The extent of underrecognition and under-notification should be thoroughly investigated to identify the real burden of pertussis in Italy.

Conflict of interest

A E Tozzi received grants for clinical studies by Wyeth/Pfizer (conjugate pneumococcal vaccine), Glaxo SmithKline (measles mumps rubella varicella vaccine) and Sanofi Pasteur MSD (hexavalent vaccine).

Authors' contributions

Michaela V.Gonfiantini: designed the study, coordinated and carried out data collection and data analysis, drafted the initial manuscript, and approved the final manuscript as submitted.
Emanuela Carloni: carried out data analysis, drafted the initial manuscript, and approved the final manuscript as submitted.
Francesco Gesualdo: collaborated in data analysis, revised the manuscript, and approved the final manuscript as submitted.
Elisabetta Pandolfi: collaborated in data analysis, critically reviewed the manuscript, and approved the final manuscript as submitted.
Eleonora Agricola: collaborated in data analysis, critically reviewed the manuscript, and approved the final manuscript as submitted.
Elvira Rizzuto: provided data and analysis on the epidemiology of pertussis in Italy based on routine surveillance, critically reviewed the manuscript, and approved the final manuscript as submitted.
Stefania Iannazzo: provided data and analysis on the epidemiology of pertussis in Italy based on routine surveillance, critically reviewed the manuscript, and approved the final manuscript as submitted.
Marta L. Ciofi degli Atti: carried out data collection and analysis on the paediatric sentinel surveillance system, critically reviewed the manuscript, and approved the final manuscript as submitted.
Alberto Villani: reviewed and revised the manuscript, and approved the final manuscript as submitted.
Alberto E. Tozzi: conceptualised and designed the study, coordinated and supervised data analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

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Laboratory capability and surveillance testing for Middle East respiratory syndrome coronavirus infection in the WHO European Region, June 2013

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Since September 2012, over 90 cases of respiratory disease caused by a novel coronavirus, now named Middle East respiratory syndrome coronavirus (MERS-CoV), have been reported in the Middle East and Europe. To ascertain the capabilities and testing experience of national reference laboratories across the World Health Organization (WHO) European Region to detect this virus, the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe conducted a joint survey in November 2012 and a follow-up survey in June 2013. In 2013, 29 of 52 responding WHO European Region countries and 24 of 31 countries of the European Union/European Economic Area (EU/EEA) had laboratory capabilities to detect and confirm MERS-CoV cases, compared with 22 of 46 and 18 of 30 countries, respectively, in 2012. By June 2013, more than 2,300 patients had been tested in 23 countries in the WHO European Region with nine laboratory-confirmed MERS-CoV cases. These data indicate that the Region has developed significant capability to detect this emerging virus in accordance with WHO and ECDC guidance. However, not all countries had developed capabilities, and the needs to do so should be addressed. This includes enhancing collaborations between countries to ensure diagnostic capabilities for surveillance of MERS-CoV infections across the European Region.

Background

In September 2012, a novel coronavirus was first characterised at the Erasmus Medical Center (EMC), Rotterdam, the Netherlands, by genome sequencing of a viral isolate from a patient in Saudi Arabia with severe pneumonia [1] and was later designated as Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. Coronaviruses are enveloped viruses with a positive-sense, single-stranded RNA genome. They can cause respiratory and enteric infections in humans and animals [3,4]. Coronaviruses known to infect humans include the human hCoV-229E and hCoV-NL63 alphacoronaviruses, as well as hCoV-OC43, hCoV-HKU1 [5], severe acute respiratory syndrome (SARS)-CoV [6] and now MERS-CoV betacoronaviruses [1]. As of 22 July 2013, there have been 90 laboratory-confirmed cases of human infection with MERS-CoV in the Middle East, North Africa and Europe, including 45 deaths. Of these, nine confirmed cases and five deaths directly or indirectly linked to the Middle East had been reported by four countries in the European Region (France, Germany, Italy and the United Kingdom (UK)) [7,8].

As per the current testing guidance of the World Health Organization (WHO), screening and confirmation of the MERS-CoV infection is based on detection of viral RNA by reverse transcription-polymerase chain reaction (RT-PCR) and sequencing [9]. The testing algorithm includes a two-step approach: (i) screening, targeting the region upstream of the *E* gene (*upE* RT-PCR [10],) and (ii) confirmation, targeting the open reading frame *1a* (*ORF1a* RT-PCR [11]). Alternatively, screening and confirmatory testing could be done by targeting other specific regions in the MERS-CoV genome, such as *RdRp* and/or *N* genes, and sequence determination of the amplified product [11,12]. Surveillance recommendations for human MERS-CoV infections are available from WHO [13] and the European Centre for Disease Prevention and Control (ECDC) [14]; an overview of these and other recommendations for the investigation of MERS-CoV cases is available in Pebody et al. [15]. Any probable or confirmed case should be rapidly reported to national authorities to enable appropriate public health measures. National authorities must notify WHO under the International Heath Regulations (IHR) of any probable and/or confirmed case, and EU/EEA countries may simultaneously report via the EU/EEA Early Warning and Response System (EWRS).

Since laboratories are often in the front-line in the detection of emerging pathogens, ECDC jointly with WHO Regional Office for Europe conducted a rapid

survey in November 2012 to ascertain the capabilities of laboratories across the WHO European Region to detect MERS-CoV [16]. Results showed that 22 of 46 countries in the WHO European Region, including 18 of 30 EU/EEA countries, had laboratory capability to detect and confirm cases of MERS-CoV. The results also indicated the rapid development of diagnostic capabilities in the responding countries. Since the time of the survey, the epidemiological situation of MERS-CoV has evolved [7,8], including a 10-fold increase of confirmed cases as well as new travel-related cases and transmission to secondary cases in Europe and elsewhere. Moreover, new diagnostic assays, including molecular and serological assays have been developed [11,17,18].

To determine the current level of MERS-CoV diagnostic capabilities in the Region and assess the recent testing practices in relation to national and international surveillance guidance, ECDC and WHO Regional Office for Europe initiated a follow-up survey in June 2013. The results of this survey are presented here.

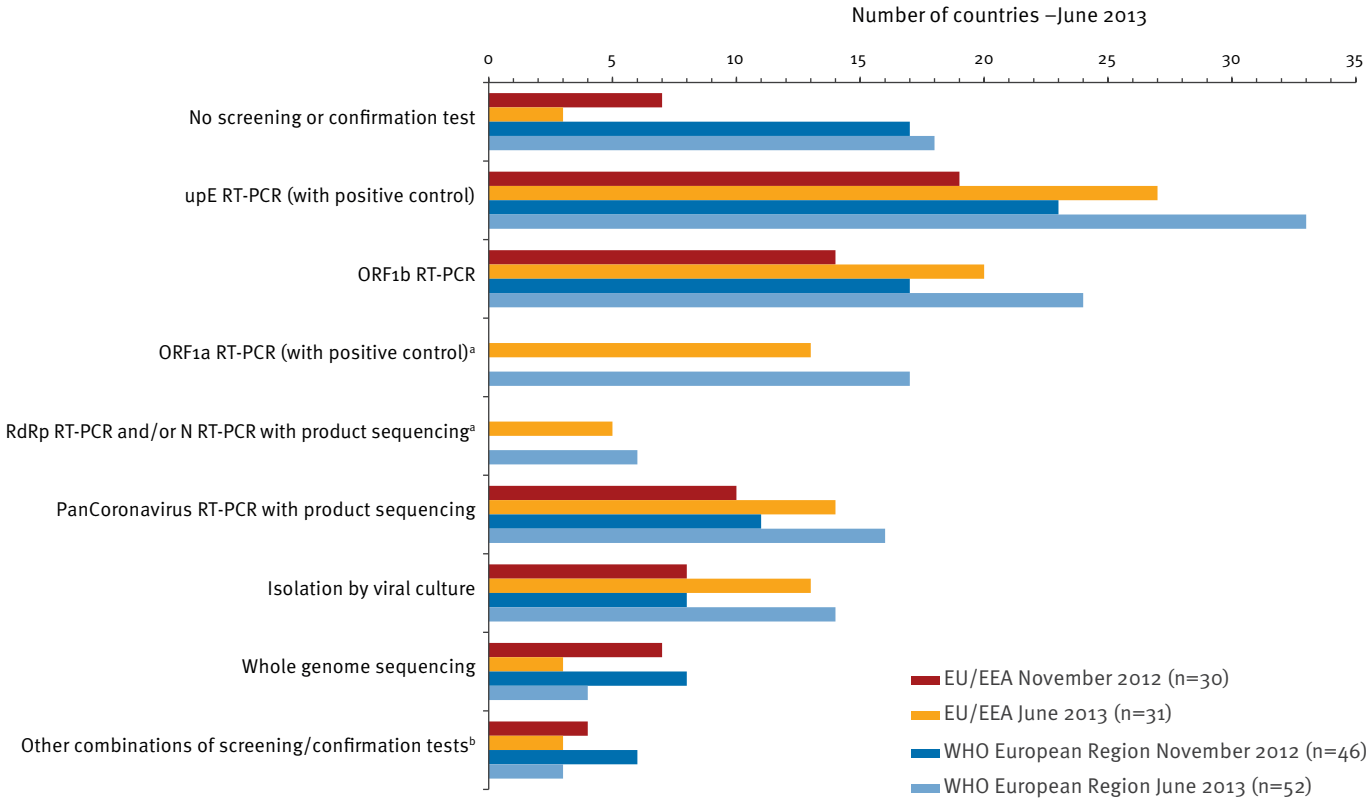
Survey of MERS-CoV detection and confirmation capabilities

The survey covered the following four areas: (i) availability of laboratory tests for detection and characterisation of MERS-CoV from human specimens; (ii) criteria used for laboratory testing and case ascertainment in relation to national, EU and international guidance; (iii) testing experience and outcome to date per country; and (iv) needs for laboratory support from ECDC and/or WHO.

The survey was administered to all countries in the WHO European Region including 53 Member States and two States Parties to the IHR (Liechtenstein and the Holy See), including the 31 EU/EEA countries. The ECDC sent the survey request by email to the National Microbiology Focal Points of the EU/EEA countries and to contact points for laboratories in the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD). The WHO Regional Office sent the survey by email to EuroFlu National Focal Points from National Influenza Centres (NICs) in non-EU/EEA countries and institutions responsible for MERS-CoV testing identified during the first survey.

Figure 1

Progressive implementation of laboratory tests for detection and confirmation of Middle East respiratory syndrome coronavirus in the World Health Organization European Region, by country, November 2012–June 2013 (n=52)



EU/EEA: European Union/European Economic Area; RdRP: RNA-dependent RNA polymerase; RT-PCR: reverse transcription-poymerase chain reaction; WHO: World Health Organization.

[a] Data for November 2012 when these tests were not yet developed.

[b] Other combinations of screening/confirmation tests include in-house-developed assays as well as the use of commercially available RT-PCR kits for human coronaviruses.

Data were collected until 28 June 2013 and were validated by the survey respondents on 5 August 2013.

Survey results

The survey captured data from 52 of 55 countries in the WHO European Region including all 31 EU/EEA countries, giving response rates of 94% and 100%, respectively. The survey captured capabilities of 72 laboratories in the Region, of which 36 laboratories from 34 countries were WHO-recognised NICs and 30 laboratories from 21 countries were partners of ENIVD.

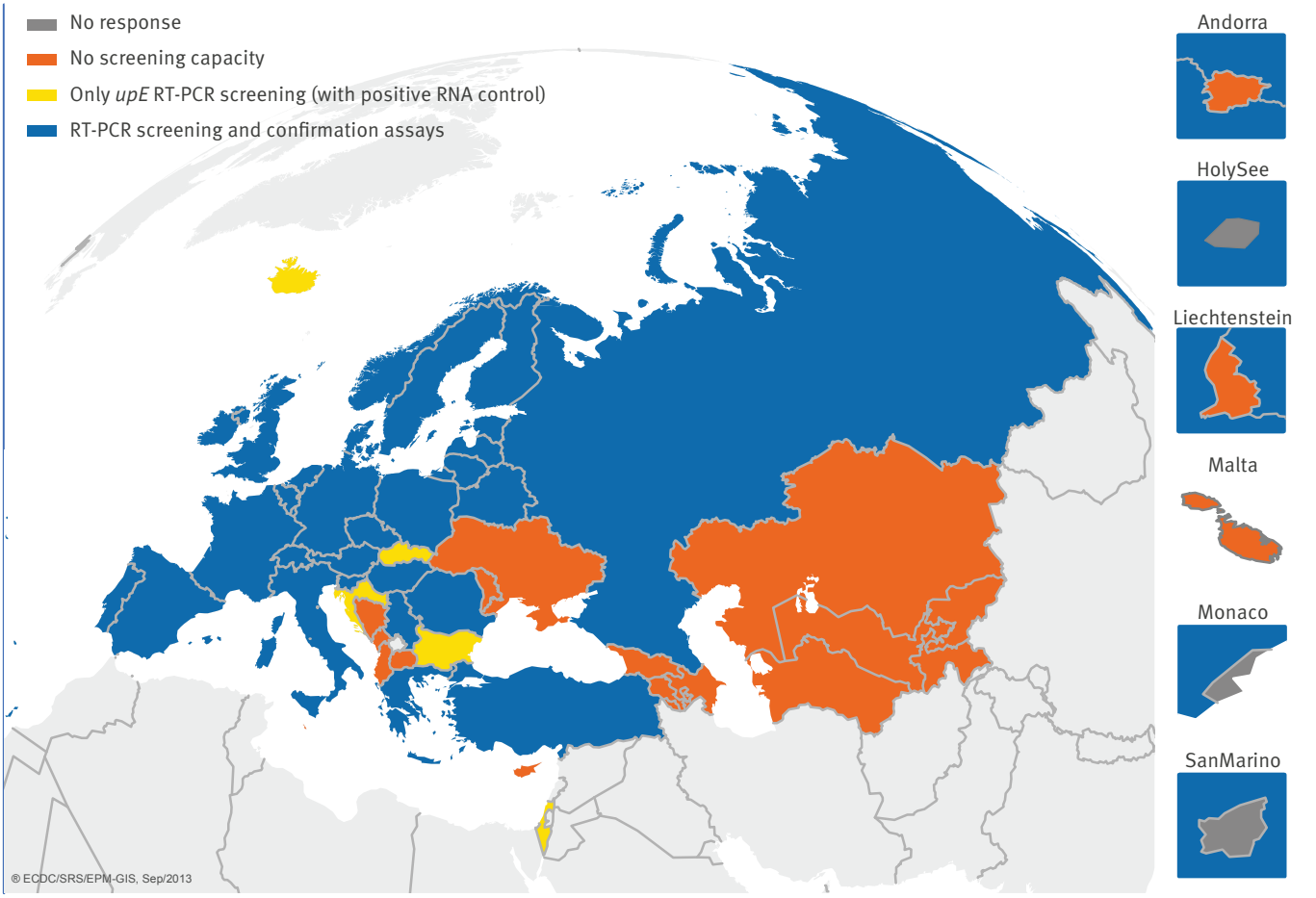
Availability of assays for MERS-CoV laboratory testing

Data showed that 33 of 52 countries in the WHO European Region and 27 of 31 EU/EEA countries had implemented *upE* RT-PCR screening tests with a positive control. This assay was available in 51 laboratories in the WHO European Region and 41 laboratories in the EU/EEA countries. The most frequently implemented confirmation test was RT-PCR for *ORF1b*, which was available in 24 of 52 countries in the WHO European Region and 20 of 31 EU/EEA countries. Confirmation using RT-PCR targeting *ORF1a* was available in 17 of 52 and 13 of 31 countries, respectively. Application of *RdRp* and/or *N* gene RT-PCR followed by sequence determination was confirmed by six of 52 and five of 31 countries, respectively. Five of the responding countries in the WHO European Region indicated that they had serological assays for MERS-CoV testing available. These tests included IgG and IgM immunofluorescence assay, Western blot against recombinant N protein, serum neutralisation tests [11,17], or protein microarray using in-vitro expressed coronavirus spike proteins as antigens [18]. Figure 1 shows the progressive implementation of screening/confirmation tests between November 2012 and June 2013 for MERS-CoV in the responding countries.

Based on the information on available tests and using the WHO interim case definition [12], we analysed the different degrees of MERS-CoV diagnostic capabilities in the region (Figure 2). We found that 29 of 52 countries in the Region and 24 of 31 EU/EEA countries had the capability to screen and confirm human MERS-CoV cases, compared with 22 of 46 and 18 of 30 respectively, reported in the November 2012 assessment [16]. Only screening using *upE* RT-PCR was available in five and four of the responding countries in the Region and EU/EEA, respectively. Seventeen countries had no national-level capability for MERS-CoV detection and confirmation; most were located in the south-eastern

Figure 2

Laboratory capabilities for detection and confirmation of Middle East respiratory syndrome coronavirus in the World Health Organization European Region, by country, June 2013 (n=52)



and eastern European part of the Region. All three EU/EEA countries without MERS-CoV screening/confirmation capability reported that referral arrangements were in place for shipment of specimens to other laboratories in the EU.

Recommendations used for testing and testing experience by indication and type of specimens

The recommendations for MERS-CoV testing that were reported as being applied at national level were the WHO interim surveillance recommendations [13], followed by 36 of 52 countries in the Region and 23 of 31 EU/EEA countries, and the ECDC surveillance recommendations [14], used in 22 of 52 and 18 of 31 countries, respectively. Other testing guidance documents used were issued by national authorities (16 of 52 and 10 of 31 countries, respectively) and two countries followed the recommendations of the United States Centers for Disease Control and Prevention.

Following the respective recommendations, between the period of September 2012 and June 2013, 23 of 52 countries in the Region and 19 of 31 EU/EEA countries reported testing of human samples for MERS-CoV. The number of patients tested varied by country as indicated in Figure 3 and Table 1. Note that the relatively high numbers of patients tested in Belgium and Italy were due to screening for MERS-CoV being included in routine testing as part of surveillance for severe acute respiratory infections (SARI). The majority of countries with testing experience tested between one and 10 patients during the studied period (13 of 23 countries in the Region and 11 of 19 EU/EEA).

Nearly 80% of all samples tested were specimens from the upper respiratory tract (Table 1). Specimens from the lower respiratory tract were used in 17% of all samples tested. Other types of specimens reported included urine and serum samples.

Excluding 1,812 patients from Belgium and Italy tested for MERS-CoV as part of the routine surveillance scheme for SARI, testing of 522 patients in the 23 countries followed the indications recommended for surveillance. In 367 cases, one of the main reasons reported for triggering testing was the symptoms exhibited by the patient. Recent travel to the Middle East in patients with pneumonia or acute respiratory distress syndrome (ARDS) was reported as a reason for testing in 319 cases, and developing of respiratory symptoms following close contact with a confirmed or probable case of MERS-CoV infection in 114 cases. Other reasons for

Figure 3

Number of patients tested for Middle East respiratory syndrome coronavirus in the World Health Organization European Region, by country, September 2012–June 2013 (n=52)

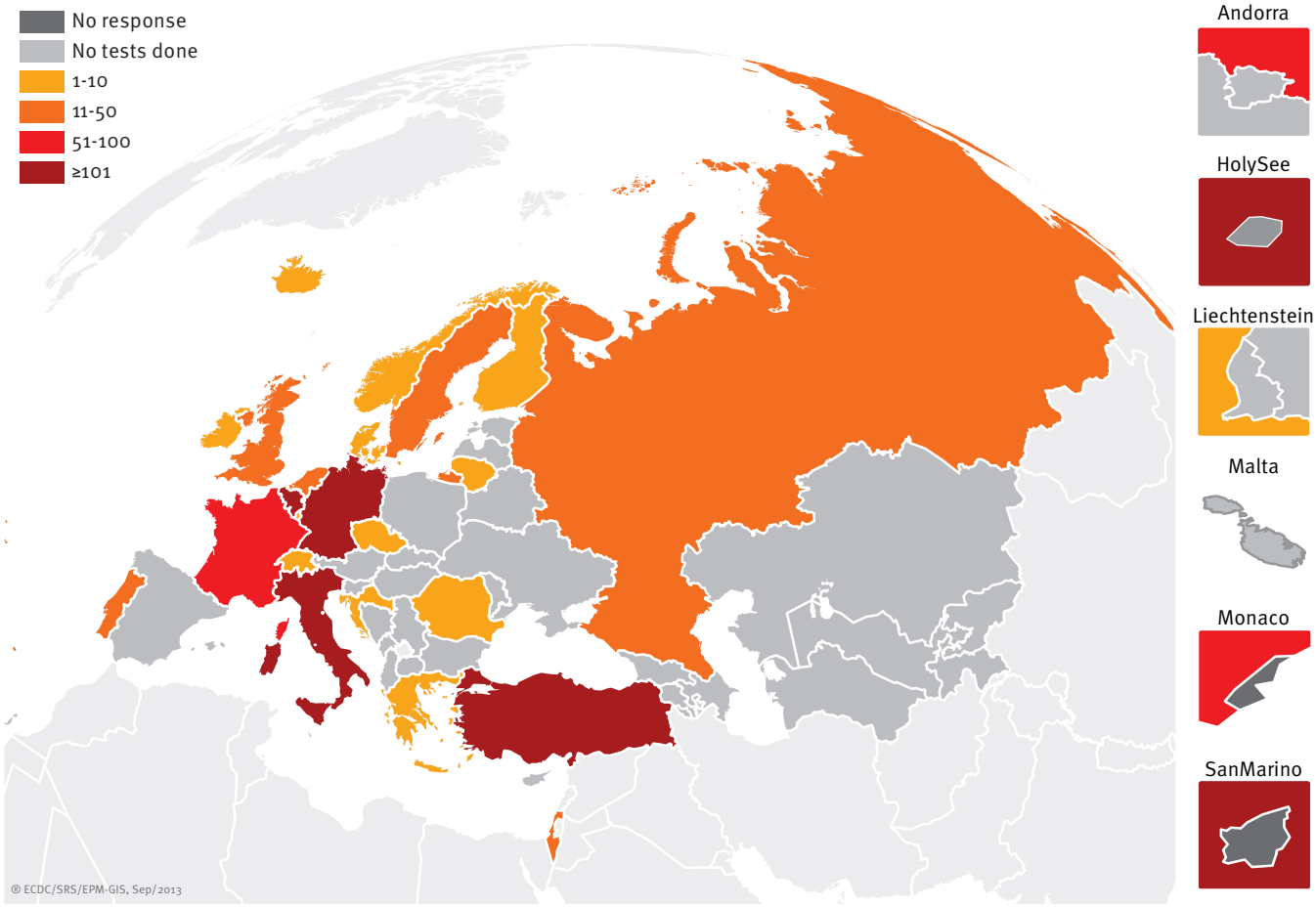


Table 1

Testing experience for Middle East respiratory syndrome coronavirus in the World Health Organization European Region, per country, June 2013 (n=52)

Country	Total number of patients tested (positive	Patients tested per criterion[a]				Specimen type[b]		
		Contact	Travel	Symptoms	Other	Upper respiratory	Lower respiratory	Other
Belgium	861 (0)	0	1	861	0	*861*	0	0
Croatia	1 (0)	0	1	1	0	1	0	0
Czech Republic	2 (0)	0	2	1	1	2	1	0
Denmark	10 (0)	0	10	0	0	*10*	0	0
Finland	2 (0)	0	2	2	0	1	1	0
France	52 (2)	7	45	52	0	99	40	0
Germany	108 (2)	85	5	5	0	7	6	85
Greece	3 (0)	1	2	3	0	3	2	0
Iceland	1 (0)	0	1	1	0	1	0	0
Ireland	2 (0)	1	1	2	0	2	2	0
Israel	29 (0)	0	13	16	0	29	6	0
Italy	1,001 (3)	14	10	996	25	732	269	0
Lithuania	1 (0)	0	1	0	0	1	0	0
Luxembourg	6 (0)	0	0	6	0	6	0	0
The Netherlands	12 (0)	4	12	9	0	12	1	1
Norway	2 (0)	0	2	1	0	3	0	0
Portugal	25 (0)	0	0	25	0	25	0	0
Romania	1 (0)	0	1	1	0	1	0	0
Russian Federation	11 (0)	0	10	11	1	9	6	4
Sweden	16 (0)	0	14	0	2	13	7	16
Switzerland	6 (0)	1	6	6	0	6	1	0
Turkey	140 (0)	0	140	140	0	97	51	0
United Kingdom	42 (4)	1	40	40	0	42	28	0
Total	2,334 (11)	114	319	2,179	29	1,963	421	106

[a] Criterion 'Contact' refers to close physical contact with a confirmed or probable MERS-CoV case; 'Travel' refers to travel to the Arabian peninsula or neighbouring countries within 10 to 14 days before onset of illness; 'Symptoms' refers to febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory distress syndrome).

[b] Multiple specimens were collected for some patients.

Table 2

Needs for laboratory support for Middle East respiratory syndrome coronavirus detection and confirmation in the World Health Organization European Region, by country, June 2013 (n=52)

Area of support	EU/EEA (n = 31)	WHO European Region (n=52)
No support needed	11	13
Provision of primers and probes	8	23
Provision of positive control material for RT-PCR	15	32
Assistance with shipment abroad for MERS-CoV testing	7	16
Other type of support	8	12

EU/EEA: European Union/European Economic Area; MERS-CoV: Middle East respiratory syndrome coronavirus; WHO: World Health Organization.

testing included patients in intensive care with severe acute respiratory infections for which no other causative infectious agents were detected. More than 300 patients tested for MERS Co-V had fulfilled at least two of the criteria for testing. Countries that performed the largest part of testing were Turkey, Germany, France and the UK.

Need for laboratory support from ECDC and/or WHO

When asked about laboratory support needed, 75% of the reporting countries in the Region and 65% of those in the EU/EEA identified needs for laboratory diagnostic support from ECDC and/or WHO (Table 2). The most frequently stated need was continued provision of positive control material for RT-PCR (63% countries in the Region and 48% of EU/EEA countries). Other needs included training of laboratory personnel, provision of RT-PCR reagents and consumables, assistance with viral culture and serological assays.

Discussion

The findings of this study show that 10 months after sequence information for the first reported MERS-CoV case was made available [1], 29 of 52 countries in the WHO European Region and 24 of 31 EU/EEA countries have developed laboratory capabilities to detect and confirm MERS-CoV cases. Compared with the assessment of these capabilities in November 2012 [16], an additional seven countries in the Region and six in the EU/EEA had implemented MERS-CoV detection and confirmation capability by June 2013. While case confirmation was done mainly by *ORF1b* RT-PCR and whole genome sequencing in November 2012 [16], several additional specific assays are now in use in Europe's expert microbiology laboratories (RT-PCR for *ORF1a*, *RdRp* and the *N* gene, followed by sequencing). Moreover, 23 laboratories in 14 countries in the Region are now capable of isolating and identifying MERS-CoV by culture, compared with 16 laboratories in eight countries in November 2012. Interestingly, the number of countries using other combinations of screening/confirmation tests as well as whole genome sequencing has decreased as international testing recommendations has become available and commonly accepted methods for screening and confirmation have been implemented.

The rapid increase in diagnostic capabilities described here is due to dedicated efforts at national level, to support from WHO via its network of NICs and from ECDC via dedicated laboratory networks (e.g. ENIVD) and to other EU initiatives. The European Virology Archive (EVA) for example, allowed laboratories to receive positive control material for the upE and *ORF1a* RT-PCR assays to set up the necessary MERS-CoV diagnostic assays.

However, a large proportion of laboratories still need support for the provision of positive control material as well as primers and probes for RT-PCR, and assistance with shipment abroad for MERS-CoV testing. These remaining needs are of concern, especially for countries neighbouring MERS-CoV endemic areas. Therefore, WHO is currently analysing the factors hampering the uptake of MERS-CoV diagnostic assays in this part of the Region. The aim of this analysis is to set up a mechanism which ensures Region-wide deployment of laboratory diagnostic assays for MERS-CoV.

ECDC is currently supporting an external quality assessment scheme for MERS-CoV via ENIVD, addressing laboratory performance and pending gaps in capabilities for detection and confirmation of MERS-CoV in the Region. Thus, building on existing WHO and EU laboratory networks, the two agencies will strive to maintain and further enhance diagnostic capabilities for MERS-CoV.

Our survey collected information on the types of clinical specimens used for testing. However, we did not collect specific information on what proportion of specimens were used for MERS-CoV diagnosis vs follow-up of diagnosed patients or monitoring of viral loads. The majority of specimens used for MERS-CoV testing were obtained from the upper respiratory tract which, according to preliminary reports, may contain lower viral loads than specimens from the lower respiratory tract [19,20]. Therefore, it is advisable to increase awareness among healthcare providers of the benefits of obtaining specimens from the lower respiratory tract when possible, particularly in case of disease progression, and to integrate this recommendation into national laboratory testing algorithms.

Importantly, the improved capabilities for MERS-CoV case confirmation were accompanied by increased testing in the European Region: since September 2012, over 2,300 patients have been tested in 23 countries. Apart from two countries that extended MERS-CoV detection tests to SARI patients irrespective of travel or contact history, the vast majority of countries focused on travellers with pneumonia or ARDS upon recent return from the Middle East and patients with close contact with a confirmed or probable case of MERS-CoV infection, in compliance with international guidance. However, the number of patients fulfilling these clinical and epidemiological criteria during the study period was not collected and we can therefore not estimate the case-finding bias per country and across the Region as a whole. In September 2013, WHO published updated recommendations for laboratory testing of MERS-CoV [9]. These recommendations highlight the need for intensified efforts to validate serological tests for case finding and serological studies in risk groups and targeted populations. At the time of our study, existing serological tests had been validated against small numbers of convalescent sera, and there is no consensus on the interpretations of the results. WHO, ECDC and their networks will investigate possibilities to enhance the collaboration with countries in affected regions which would provide a platform for validating

serological assays. At the time of this study, only five countries indicated that they had the capability to perform assays for MERS-CoV-specific antibody detection.

After submission of this manuscript, three countries in the Region reported cases of MERS-CoV in returning travellers or residents of countries of the Middle East: Greece (one case, April 2014), the Netherlands (two cases, May 2014) and Austria (one case, September 2014). In total 14 laboratory-confirmed cases have been reported since April 2012. More information is available in the updated ECDC rapid risk assessment from August 2014 and the epidemiological update from October 2014 [21,22].

In order to provide laboratories with the opportunity to assess their capabilities, a first external quality assurance (EQA) panel for the detection of MERS-CoV by PCR was organised in spring 2014 by ENIVD with support of ECDC and WHO. Laboratories in 33 countries the Region participated in this scheme. A feasibility of a new global EQA scheme is currently being explored by WHO. A training for national public health institutes on laboratory preparedness and rapid establishment of detection assays for emerging respiratory pathogens will be conducted in November 2014. Based on the new evidence on MERS-CoV infection and new information on diagnostic assays, WHO issued updates of surveillance, case definition and laboratory recommendations [23,24,25]. The major change compared with the previous version is that a patient may be considered as a confirmed case if a four-fold rise in neutralising antibody titre can be demonstrated, regardless of any PCR results.

Conclusion

The decision taken at the second meeting of the Emergency Committee convened by the WHO Director-General on 17 July 2013 under the IHR was that the current outbreak of MERS-CoV is not a Public Health Emergency of International Concern (PHEIC) [26]. Importantly however, it was noted that while the PHEIC conditions had not been met, WHO, ECDC and Member States should continue to be vigilant in their surveillance for MERS-CoV. Although only fourteen confirmed MERS-CoV cases have been identified in the Region since April 2012, the substantial amount of testing reported here serves as a reassurance of the existing laboratory support to MERS-CoV surveillance. As the present study shows, there is robust capability for detection and confirmation of human MERS-CoV cases in the EU/EEA. However, one third of the countries of the WHO European Region, mainly in the south-east and eastern part of the Region, are still lacking MERS-CoV diagnostic capabilities. Therefore, efforts continue to address the remaining laboratory needs in order to ensure MERS-CoV detection and confirmation capability needed for active surveillance of this emerging disease in Europe.

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Conflict of interest

None declared.

Authors' contributions

None declared.

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Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008–2011

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Invasive pneumococcal disease (IPD) is a notifiable disease in the Region of Madrid. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for children and adults aged two years or over with a high risk of disease, and for all adults aged 60 and over. We describe the evolution of IPD incidence from 2008 to 2011 in people aged 60 years and over and PPV23 vaccine effectiveness (VE). VE is estimated using both the screening method and indirect cohort method. The incidence of IPD varied from 20.0 in 2008 to 15.2 per 100,000 inhabitants in 2011 (RR: 0.8; 95% CI: 0.6–0.9). Adjusted VE estimated with the screening method was 68.2% (95% CI: 56.2–76.9). VE with the Broome method was 44.5% (95% CI: 23.8–59.6) for all PPV23 serotypes, and 64.4% (95% CI: 45.2–76.8) for PPV23 serotypes not included in conjugate vaccines. VE was lower in patients aged 80 years and older (25.5%; 95% CI:-23.2 to 55.0) and those with high-risk medical conditions (31.7%; 95% CI: -2.2 to -54.4). Adjusted VE was 44.5% (95% CI: 19.4-61.8) within 5 years of vaccination and 32.5% (95% CI: -5.6 to 56.9) after 5 years. These results are compatible with current recommendations for PPV23.

Introduction

Pneumococcal disease has high morbidity and mortality rates worldwide, mainly in children and in the elderly. The fatality rates for pneumococcal bacteraemia can reach 15–20% in adults and 30–40% in the elderly [1]. The incidence of invasive pneumococcal disease (IPD) is highly variable according to geographical region, ranging from 8 to 34 cases per 100,000 inhabitants [2].

The human nasopharynx is the natural ecosystem for *Streptococcus pneumoniae*. Young children are the main reservoir. The prevalence of carriers ranges from 27% in developed countries to 85% in developing ones [1]. Many conditions and behaviours that alter the host's immunological capacity pave the way for a predisposition to the disease, including alcoholism, cigarette smoking, chronic lung disease, congestive heart failure, diabetes mellitus, malignant neoplasm, renal disease, liver disease, immunosuppression and recent hospitalisation [3].

Since the early 1980s, a 23-valent pneumococcal polysaccharide vaccine (PPV23) has been available and recommended in many industrialised countries for high-risk groups, including adults aged 65 years and over [1,2]. However, the efficacy of this vaccine remains controversial. The results of meta-analyses and clinical studies agree that there is a protective effect against IPD and pneumonia in healthy adults. However, its efficacy has not been proven in patients with risk factors for IPD [4,5]. Since 2005, the vaccine has been recommended in the Region of Madrid and paid for with public funds for adults and children over the age of two years who are at high risk of disease, and for all adults aged 60 years and over.

Since 2000, conjugate pneumococcal vaccines have been available for use in young children. Following their routine use, herd immunity, an indirect effect of protection against the disease, has been observed in unvaccinated individuals [6-8]. In November 2006, the 7-valent pneumococcal conjugate vaccine (PCV7) was included in the childhood vaccination schedule of the Region of Madrid, using public funding. This vaccine was replaced by the 13-valent pneumococcal conjugate vaccine (PCV13) in June 2010. The mean vaccination coverage of the pneumococcal conjugate vaccines for children at two years of age from 2008 to 2011 was 94.4%. In July 2012, public funding of this vaccine was stopped due to budgetary reasons, except for people at high risk of disease.

IPD has been a notifiable disease in the Region of Madrid since February 2007. Data are collected through a population-based epidemiological surveillance system.

This study describes the evolution of the incidence and the epidemiological characteristics of the IPD cases in people aged 60 years and over living in the Region of Madrid, and the effectiveness of PPV23 vaccine during from 2008 to 2011.

Methods

Study population

The analysis focuses on cases of IPD registered in the Surveillance System of the Region of Madrid (based on mandatory laboratory and clinical reporting), in adults aged 60 years and over, living in the Region and whose symptoms appeared between 2008 and 2011.

Individualised data were collected with a standardised questionnaire that included sociodemographic features, clinical data (date of symptom onset, clinical presentation, evolution and high-risk medical conditions), laboratory data and vaccination status. Based on the national recommendations [9], high-risk medical conditions were considered, including: immunodeficiency, cranial trauma, cranial surgery, cerebrospinal fluid leak, splenectomy, chronic liver disease, chronic heart disease, chronic kidney disease, chronic respiratory disease, cancer, HIV, diabetes mellitus and alcoholism. Only one clinical presentation and one high-risk medical condition were considered for each patient. The clinical data were obtained from attending physicians and clinical records. Vaccination status was collected by consulting the Region of Madrid's vaccination register.

Laboratory methods

An IPD case was defined as an infection with haematogenous spread of the pathogen, causing different clinical syndromes, where *S. pneumoniae* was identified in samples from places normally sterile by isolation, PCR or antigen detection. Serotype identification was centralised in the Madrid Regional Public Health Laboratory, and was performed by the latex agglutination test (Pneumotest-Latex, Statens Serum Institut, Copenhagen, Denmark) and the Quellung reaction.

Statistical methods

Individuals were considered to be vaccinated if date of vaccination with PPV23 was at least 15 days before the onset of symptoms. Differences between vaccinated and unvaccinated patients were estimated. Variables associated with the disease were analysed by vaccine serotypes. Chi-squared test or Fisher's exact test were used to compare proportions.

Overall annual incidence rates were calculated per 100,000 inhabitants, as well as specific incidence rates by sex, age group, clinical presentation, and vaccine serotype. Age was coded into three age groups: 60–69, 70–79 and 80 years or older. The incidence was estimated for PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), PCV13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) and PPV23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). The rates were compared using relative risk (RR) and its confidence interval (CI) at 95%. The continuous census of inhabitants of the Community of Madrid was used as the reference population [10].

Vaccine effectiveness (VE) was calculated using two methods: the screening method and the indirect cohort (Broome) method. VE is interpreted as the proportion of cases prevented in vaccinated people by the effect of vaccination. Based on VE, we estimated the number of cases prevented in the study period. The screening method [11] is based on the comparison of the proportion of vaccinated cases with the proportion of the vaccinated population. The approach described by Farrington [12] was used. This allows adjustment of VE by possible confounders (sex, age group) using logistic regression models. The model requires the vaccination coverage of each of the subgroups of analysis. Data on vaccination coverage were obtained from the Region of Madrid's vaccination register.

On the other hand, the Broome method [13] is based on comparison of the vaccination odds of IPD cases due to vaccine serotypes with the vaccination odds of IPD cases due to non-vaccine serotypes, the latter serving as the control group. The VE was calculated as (1 - odds ratio) x 100. VE was estimated for the group of all serotypes included in PPV23, and then for the group of serotypes that are found in PPV23, but are not found in the conjugate vaccines (that is, conjugate vaccine serotypes were excluded from the analysis). Serotype-specific VE was assessed for serotypes included in PPV23 that had been identified in at least 30 cases. In this analysis the other PPV23 serotypes were excluded. To estimate VE by time elapsed since vaccination, vaccination status was classified as unvaccinated, vaccinated within the previous 5 years, and vaccinated more than 5 years ago. Adjustment for potential confounders (sex, age, high-risk medical condition and year of symptom onset) was made by logistic regression. Statistical significance was set at $p<0.05$. The analyses were performed using PASW Statistics, version 18.0.2 (SPSS Inc., Chicago, IL).

Results

Between 2008 and 2011, 2,432 cases of IPD were registered in the Region of Madrid, of which 864 (35.5%) were in adults aged 60 years and over. The characteristics of IPD cases in people aged 60 years and over are shown in table 1. A slight predominance of men was seen (480 cases, 55.6%). Pneumonia and/or empyema was the main clinical presentation (537 cases, 62.2%). A total of 368 cases (42.6%) had received PPV23 and 519 (60.1%) had high-risk medical

conditions associated with pneumococcal disease. 46.8% of cases with high-risk medical conditions had been vaccinated. Immunodeficiency and/or cancer was the main high-risk medical condition (161 cases, 18.6%), followed by chronic respiratory disease (151 cases, 17.5%). Serotyping was available in 799 cases (92.5%). The main serotypes identified were the following: 3 (119 cases, 14.9%), 19A (101 cases, 12.6%), 7F (59 cases, 7.4%), 1 (42 cases, 5.3%) and 8 (40 cases, 5.0%). In 588 cases (73.6%) a serotype included in PPV23 was identified, in 89 (11.1%) a serotype included in PCV7 and in 431 (53.9%) a serotype included in PCV13.

Table 1

Characteristics of invasive pneumococcal disease cases in patients aged 60 years and over by vaccination status, Region of Madrid, Spain, 2008–2011, n=864

	Total cases (%)	Vaccinated cases (%)	Unvaccinated cases (%)	p value
Sex				
Men	480 (55.6)	220 (59.8)	260 (52.4)	0.031[a]
Women	384 (44.4)	148 (40.2)	236 (47.6)	0.031[a]
Total	**864 (100.0)**	**368 (100.0)**	**496 (100.0)**	
Age				
60–69 years	266 (30.8)	82 (22.3)	184 (37.1)	0.000[a]
70–79 years	285 (33.0)	135 (36.7)	150 (30.2)	0.046[a]
› 64 years	727 (84.1)	345 (93.8)	382 (77.0)	0.000[a]
› 79 years	313 (36.2)	151 (41.0)	162 (32.7)	0.011[a]
Total	**864 (100.0)**	**368 (100.0)**	**496 (100.0)**	
Clinical presentations				
Pneumonia/empyema	537 (62.2)	223 (60.6)	314 (63.3)	0.417
Bacteraemia	125 (14.5)	51 (13.9)	74 (14.9)	0.661
Sepsis	91 (10.5)	41 (11.1)	50 (10.1)	0.615
Meningitis	59 (6.8)	28 (7.6)	31 (6.3)	0.433
Other	34 (3.9)	19 (5.2)	15 (3.0)	0.111
Unknown	18 (2.1)	6 (1.6)	12 (2.4)	0.422
Total	**864 (100.0)**	**368 (100.0)**	**496 (100.0)**	
Year				
2008	241 (27.9)	69 (18.8)	172 (34.7)	0.000[a]
2009	228 (26.4)	88 (23.9)	140 (28.2)	0.155
2010	197 (22.8)	99 (26.9)	98 (19.8)	0.013[a]
2011	198 (22.9)	112 (30.4)	86 (17.3)	0.000[a]
Total	**864 (100.0)**	**368 (100.0)**	**496 (100.0)**	
High-risk medical conditions				
Immunodeficiency/cancer	161 (18.6)	73 (19.8)	88 (17.7)	0.434
Chronic respiratory disease	151 (17.5)	73 (19.8)	78 (15.7)	0.115
Chronic heart disease	102 (11.8)	50 (13.6)	52 (10.5)	0.162
Chronic liver disease	32 (3.7)	11 (3.0)	21 (4.2)	0.338
Chronic kidney disease	21 (2.4)	9 (2.4)	12 (2.4)	0.980
Splenectomy	2 (0.2)	1 (0.3)	1 (0.2)	0.832
Head injury/cranial surgery/CSF leak	5 (0.6)	3 (0.8)	2 (0.4)	0.430
Other (diabetes, alcoholism, etc.)	45 (5.2)	24 (6.5)	21 (4.2)	0.134
Total cases with high-risk medical conditions	519 (60.1)	244 (66.3)	275 (55.4)	0.001[a]
Total	**864 (100.0)**	**368 (100.0)**	**496 (100.0)**	
Total cases serotyped	**799 (92.5)**	**348 (94.6)**	**451 (90.9)**	**0.045[a]**
Deaths (fatality rate)	**138 (16.0)**	**55 (14.9)**	**83 (16.7)**	**0.478**
TOTAL	**864 (100.0)**	**368 (100.0)**	**496 (100.0)**	

CSF: cerebrospinal fluid

[a] p<0.05

The characteristics of cases by vaccination status are shown in Table 1. Vaccinated patients were older, had a higher proportion of men, presented more high-risk medical conditions and had a higher proportion of cases serotyped.

The proportion of PPV23 serotypes was 67.2% in vaccinated cases and 78.5% in unvaccinated cases($p<0.01$). The proportion of serotypes included in PPV23 but not in conjugate vaccines was 14.7% in vaccinated and 25.5% in unvaccinated ($p<0.01$). The proportion of PCV7 and PCV13 serotypes was similar in vaccinated and unvaccinated patients. The serotypes with the highest difference in the proportion of vaccinated to unvaccinated cases were 6C, 16F, 19A, 14 and 24F (Figure).

When we compared the disease caused by PPV23 serotypes with the disease caused by the other serotypes, the only variables that showed significant differences were vaccination status and year of symptom onset. Age, sex and presence of high-risk medical conditions showed no significant differences.

In the study period, a significant increase in the proportion of vaccinated cases (28.6% in 2008 and 56.6% in 2011) was seen, as well as in the proportion of cases with high-risk medical conditions (47.7% in 2008 and 71.2% in 2011). The percentage of patients with high-risk medical conditions who were vaccinated ranged from 26.1% in 2008 to 60.3% in 2011. The percentage of IPD cases caused by PPV23 serotypes has dropped (76.9% in 2008 and 64.0% in 2011), mainly due to the percentage of cases caused by PCV7 serotypes (16.8% in 2008 and 6.3% in 2011).

The average annual incidence of IPD in patients aged 60 years and over from 2008 to 2011 period was 17.2 cases per 100,000 inhabitants, and incidence rose to 19.4 in patients aged 65 years and over. During this period, incidence was observed to fall by 24% (Table 2). Clinical presentations showing a significant decrease in the incidence were bacteraemia (42% reduction) and pneumonia/empyema (31% reduction). The decrease was more pronounced in cases caused by vaccine serotypes, being 68% for cases by PCV7 serotypes, 34% for cases by PCV13 serotypes, and 30% for cases by PPV23 serotypes (Table 2).

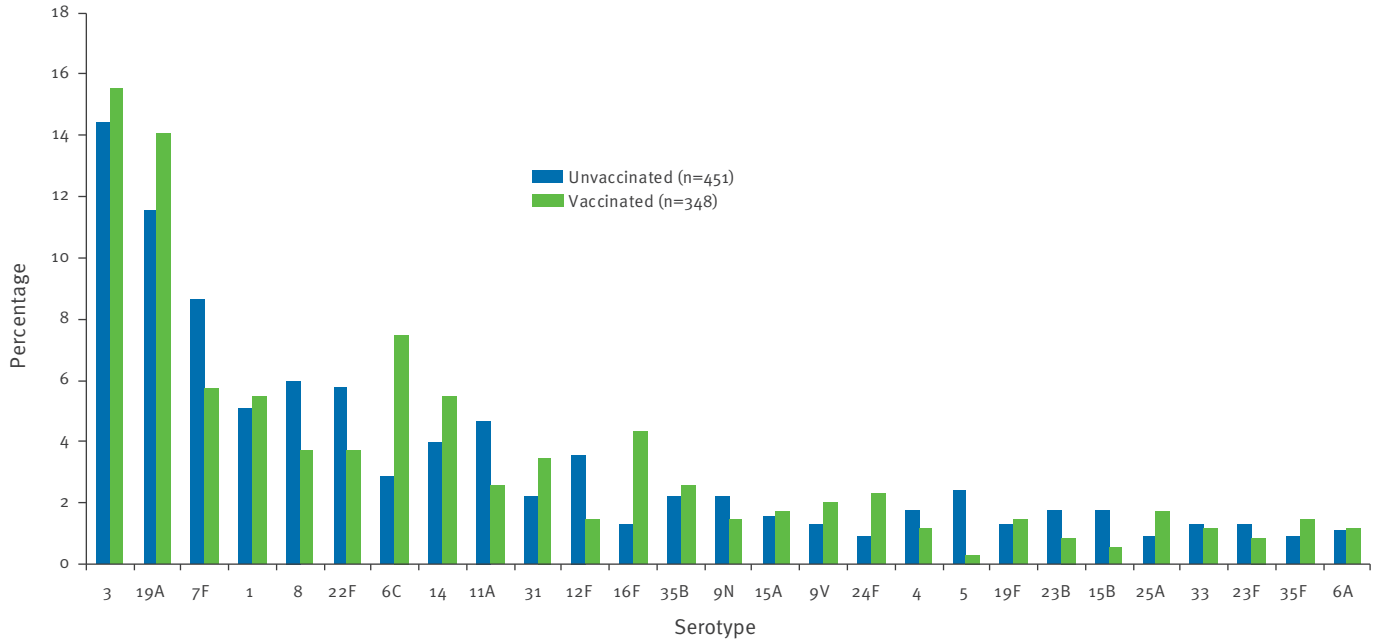
The overall PPV23 uptake for people aged 60 years and over in the study period was 52.5% (45.8% in 2008, 50.4% in 2009, 54.6% in 2010 and 59.0% in 2011). VE estimated by the screening method is shown in Table 3. The adjusted VE by sex and age group was 68.2% (95% CI: 56.2–76.9) for all IPD cases and 72.8% (95% CI: 59.1–81.8) when only the cases caused by PPV23 serotypes were considered.

The estimated effectiveness of PPV23 by the indirect cohort method was 44.5% (95% CI: 23.8–59.6) (Table 4). VE was lower in patients aged 80 years and over (25.5%; 95% CI: -23.2 to 55.0) and in patients with high-risk medical conditions (31.7%; 95% CI: -2.2 to 54.4), but these differences were not significant.

In relation to VE by time since vaccination, the adjusted PPV23 effectiveness by age, sex, year of symptom onset and presence of high-risk medical conditions was 44.5% (95% CI: 19.4–61.8) when 5 years or fewer

Figure

Distribution of the main serotypes for invasive pneumococcal disease in patients aged 60 years and over, shown by vaccination status, Region of Madrid, Spain, 2008–2011, n=799



had elapsed and 32.5% (95% CI: -5.6 to 56.9) when more than 5 years had elapsed (Table 4).

The VE increased when considering only the serotypes that are included in PPV23 but not found in the conjugate vaccines. This increase was slight when considering the serotypes included in PPV23 but not in PCV7 (VE 46.8%; 95% CI: 26.3–61.6), and greater when considering the serotypes included in PPV23 but not in PCV13 (VE 64.4%; 95% CI: 45.2–76.8). Regarding the specific serotypes included in PPV23 that had been identified in at least 30 cases, serotypes 8, 11A, 22F and 7F showed the highest VE. Serotypes 14, 19A, 3 and 1 showed no significant VE (Table 4).

Based on VE calculated by the Broome method, we estimated around 200 prevented cases of PPV23 serotypes and 100 of PPV23, non-PCV13 serotypes in this period, accounting for 7.5 and 3.7 prevented cases per 100,000 vaccinated inhabitants respectively.

Serotype 6C showed a statistically significant association with vaccination status (odds ratio (OR) 2.6; 95% CI: 1.4–5.0) and year of symptom onset (OR 1.5; 95% CI: 1.1–2.0).

Discussion

The incidence of IPD observed in our study was lower than that estimated in other countries [14-16], although it was above the European average [17]. The variability observed could be partially due to differences in the surveillance systems [18]. This incidence was also lower than that observed in other Spanish regions

Table 3

Vaccine effectiveness of 23-valent pneumococcal polysaccharide vaccine in patients aged 60 years and over, estimated by screening method, Region of Madrid, Spain, 2008–2011

	VE (%)	95% CI
Overall		
Crude VE	32.7	14.1–54.6
VE adjusted by age and sex	68.2	56.2–76.9
PPV23 serotypes		
Crude VE	40.5	28.3–59.4
VE adjusted by age and sex	72.8	59.1–81.8

PPV23: 23-valent pneumococcal polysaccharide vaccine; VE: vaccine effectiveness; CI: confidence intervals

Table 2

Annual incidence of invasive pneumococcal disease in patients aged 60 years and over, Region of Madrid, Spain, 2008–2011, and comparison between incidence in 2011 and 2008

	2008	2009	2010	2011	RR 2011/2008 (95% CI)
Total cases	19.99	15.45	15.21	15.21	0.76 (0.63-0.92)[a]
Age					
60-69	14.27	12.73	8.76	10.89	0.76 (0.55-1.06)
70-79	20.92	18.63	17.80	10.95	0.52 (0.37-0.75)[a]
› 79	30.94	30.15	26.54	30.62	0.99 (0.73-1.35)
› 64	22.34	20.73	18.04	16.94	0.76 (0.62-0.93)[a]
Sex					
Men	24.83	23.51	23.07	19.48	0.78 (0.61-1.06)
Women	16.47	14.59	9.90	12.10	0.73 (0.56-0.97)[a]
Clinical presentations					
Pneumonia/empyema	12.19	11.67	10.67	8.38	0.69 (0.54-0.88)[a]
Bacteraemia	3.73	2.33	1.80	2.15	0.58 (0.36-0.92)[a]
Sepsis	1.49	1.93	1.65	2.15	1.44 (0.80-2.61)
Meningitis	1.16	1.45	0.71	1.38	1.19 (0.59-2.40)
Other	0.75	0.48	0.55	0.92	1.24 (0.52-2.93)
Vaccine serotypes					
Serotypes PCV7	2.90	2.25	1.10	0.92	0.32 (0.16-0.61)[a]
Serotypes PCV13	9.54	10.38	8.24	6.30	0.66 (0.50-0.88)[a]
Serotypes PCV13-non PCV7	6.64	8.13	7.14	5.38	0.81 (0.59-1.12)
Serotypes PPV23	13.27	13.76	10.67	9.30	0.70 (0.55-0.89)[a]
Serotypes PPV23-non PCV7	10.37	11.51	9.57	8.38	0.81 (0.62-1.04)
Serotypes PPV23-non PCV13	3.90	3.62	2.59	3.15	0.81 (0.53-1.23)

RR: relative risk; CI: confidence interval; PCV7: 7-valent pneumococcal conjugate vaccine ; PCV13: 13-valent pneumococcal conjugate vaccine; PPV23:23-valent pneumococcal polysaccharide vaccine

[a]p<0.05

where pneumococcal vaccination is not included in the childhood immunisation schedule [19-22].

Some factors such as PCV uptake, blood culture practice, fluctuations of serotype prevalence over time and antimicrobial use may play a role in the epidemiological changes observed in IPD among adults. No important changes in these factors could be detected in the four years included in the study. The main change observed was the introduction of PCV13 in children in June 2010, which may explain the decrease of PCV13, non-PCV7 serotypes after 2010.

PPV23 vaccination shows an effect on incidence of the disease, since there is a reduction in the incidence of cases due to the serotypes included in PPV23, in accordance with the increase in PPV23 uptake. The highest reduction in incidence was for serotypes included in PCV7. This agrees with a herd immunity effect due to this vaccine [6–8] and suggests a higher impact due to the indirect effect of vaccination in children rather than by the direct effect of vaccination in people aged 60 years and older.

The VE obtained by the Broome method (44.5%) was similar to that estimated in England and Wales (48%) [23]. Adjusted VE by screening method (68.2%) was also comparable to VE seen in Australia (71%) [24], Scotland (61.7%) [25] and Catalonia (70%) [26]. VE in preventing vaccine-type IPD obtained by the screening method was greater than overall VE, with an adjusted VE of 72.8%. This agrees with the VE observed in other studies [26,27].

The differences observed in VE by age, high-risk medical condition, serotype and time since vaccination in our study are similar to those described previously [23,26,27], but were not significant because the point estimate had very wide confidence intervals. Observational studies of VE against IPD usually present lower power to stratify for these variables.

Differences in the VE estimated have been found according to the method applied [24,25]. In our study the adjusted VE by the screening method was higher than the estimations using the Broome method. These results were similar to estimates in Scotland (61.7% vs 51%) [25] and this could be due to the fact that the Broome method also uses IPD cases as a control group.

The VE observed for the disease caused by the serotypes included in PPV23 but not in the conjugate vaccines is higher than that observed for all serotypes of PPV23. This result could be due to the high prevalence in the population of serotypes common to PCV13 and PPV23 vaccines, associated with the serotype

Table 4

Vaccine effectiveness of 23-valent pneumococcal polysaccharide vaccine in patients aged 60 years and over, estimated by the indirect cohort method, Region of Madrid, Spain, 2008–2011

	Cases	Controls	VE (%)	95% CI
Serotypes PPV23	588	211	44.5	23.8–59.6
Patients aged 60-69 years	177	58	54.2	15.3–75.2
Patients aged 70-79 years	195	68	54.1	19.2–73.9
Patients aged over 79 years	213	85	25.5	-23.2–55.0
Patients without HRMC	239	80	59.9	32.7–76.1
Patients with HRMC	349	131	31.7	-2.2–54.4
<= 5 years after vaccination[a]	136	67	44.5	19.4–61.8
>5 years after vaccination[a]	97	48	32.5	-5.6–56.9
Serotypes PPV23-non PCV7	499	211	46.8	26.3–61.6
Serotypes PPV23-non PCV13	166	211	64.4	45.2–76.8
Serotype 1	42	211	31.0	-34.1–64.5
Serotype 3	119	211	30.6	-8.9–55.8
Serotype 7F	59	211	53.9	16.1–74.6
Serotype 8	40	211	64.2	25.9–82.7
Serotype11A	30	211	64.2	18.2–84.3
Serotype 14	37	211	11.9	-77.3–56.2
Serotype 19A	101	211	21.3	-26.5–51.1
Serotype 22F	39	211	58.3	14.4–79.7

PPV23: 23-valent pneumococcal polysaccharide vaccine; VE: vaccine effectiveness; CI: confidence intervals; HRMC: high-risk medical conditions; PCV7: 7-valent pneumococcal conjugate vaccine; PCV13: 13-valent pneumococcal conjugate vaccine.

[a] Adjusted by sex, age, HRMC and years of symptoms onset

replacement described after the routine use of PCV7 [8,28,29], and with the differential effectiveness by serotype, identified in other studies [23]. This would suggest that PPV23 vaccine has a reduced effectiveness in populations using the conjugate vaccine in the childhood immunisation schedule.

The higher VE observed for serotypes 8, 11A, 22F and 7F could be related to differences in vaccine response of the specific serotypes. A higher VE for serotype 7F and lower for serotypes 1 and 3 have also been observed in the study performed in England and Wales [23].

Each method has both advantages and disadvantages. The screening method is quick and simple, but it requires accurate data on vaccination coverage and vaccination status of cases [30]. In our study these data were taken from the Region of Madrid's vaccine register, which collects nominal data. The screening method allows the overall effectiveness to be estimated and is very useful for routine monitoring. However it does not allow certain risk factors to be taken into account due to the non-availability of vaccination coverage in specific groups of population [12].

The Broome method can be used on specific groups of patients, such as those who show risk factors. However, it does not allow the effectiveness for the global disease to be estimated, since the cases due to non-vaccine serotypes are used as the control group. Due to the high proportion of cases with identified serotypes (92.5%), there is no need to make any assumptions in cases with unknown serotype, avoiding any possible bias related to them. The high proportion of cases with identified serotype and the independence between data on serotype and vaccination status would exclude an important bias in the estimation of VE. This method has shown its usefulness when applied to surveillance data for this disease, showing results similar to those obtained using case–control studies [23,31,32].

The higher proportion of disease due to serotype 6C in vaccinated patients observed in our study could be due to the replacement of serotypes. There has been an increase in disease due to this serotype following the routine use of PCV7 both in carriers [33] and in cases with invasive disease [34].

One of the strengths of our study is that although it is observational and based on surveillance data, it is limited to four recent years, thus important changes in the notification, diagnosis and serotyping of cases can be ruled out.

Vaccine efficacy of PPV23 against IPD has been established in clinical trials, but in high-risk patients it has not been possible to demonstrate protection [4,5]. Observational studies have shown significant vaccine effectiveness [23-26]. PPV23 is recommended in many countries for people with high-risk medical conditions and in some countries for universal vaccination of the elderly. In England and Wales, Andrews et al. observed evidence of individual protection against PPV23 serotypes despite lack of impact on IPD incidence at the population level [23] and the UK's Joint Committee on Vaccination and Immunisation recommended continuation of PPV23 vaccination programmes for all healthy individuals aged 65 years and over [35]. Several studies of cost-effectiveness of pneumococcal vaccination in the elderly have been published [36–38] and some of them have concluded that universal programmes are more cost-effective than selective vaccination of high-risk groups [36,38].

The use of PCV13 has recently been approved for people aged 50 years and over. However, its effectiveness in preventing pneumonia and IPD has not yet been proven in clinical trials [39]. Thus, at present different institutions consider that the evidence available is insufficient to recommend the routine use of PCV13 in adults [1,40,41]. This vaccine has been recently recommended for use in adults with high-risk medical conditions [40].

In conclusion, our study shows that PPV23 is effective in preventing IPD in patients aged 60 years and older, with a higher VE in patients without high-risk medical conditions. These results are compatible with the current recommendation of PPV23. Efforts to improve PPV23 uptake should continue. Epidemiological surveillance should be continued in order to evaluate the impact on IPD incidence in adults and elderly of the indirect effects of vaccinating children with pneumococcal conjugate vaccines and the role of PCV13 in adults with high-risk medical conditions.

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Conflict of interest

MA Ordobás, MA Gutiérrez, A Arce and JC Sanz have received funding from Pfizer to attend scientific meetings. L Garcia Comas has received funding from Pfizer and Sanofi to attend scientific meetings.

Authors' contributions

MA Gutiérrez Rodríguez and MA Ordobás Gavín designed the study. E Córdoba Deorador, MD Lasheras Carbajo, JA Taveira Jiménez and F Martín Martínez made the acquisition and recording of data. D Iniesta Fornies oversaw vaccination coverage data of the Vaccination Register. JC Sanz Moreno was the microbiologist who performed the laboratory analysis. MA Gutiérrez Rodríguez, MA Ordobás Gavín, L García Comas and A Arce Arnaez reviewed the analysis and the results. MA Gutiérrez Rodríguez wrote the manuscript. All authors reviewed the manuscript and agree with results and conclusions. The final version was approved by all authors.

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