

**YELLOW FEVER VACCINE USAGE BY YELLOW FEVER
VACCINATION CENTRES IN ENGLAND, WALES, AND
NORTHERN IRELAND 2013-2015**

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PURPOSE

This report contains the results of the Annual Returns Survey of designated Yellow Fever Vaccination Centres 2013-2015 with particular focus on the following objectives to:

- Determine compliance with survey
- Identify any changes in the type of yellow fever vaccination centres
- Quantify yellow fever vaccines administered
- Determine whether the World Health Organization 2013 guidance regarding yellow fever vaccine boosters and the yellow fever vaccine shortage in the UK in 2013-2015 has affected vaccine usage
- Determine the number and nature of reported adverse events

DATA

Designated Yellow Fever Vaccination Centres (YFVC or centres from hereon) in England, Wales, and Northern Ireland were invited by email each year in January to take part in the online Annual Returns survey. Centres were given a deadline at the end of March to complete the survey for the preceding year. The number of complete responses in the annual survey varied between 2,649 and 2,868 between 2013 and 2015 (Table 1; Figure 1). The response rate increased from 71% in 2013 to 80% in 2014-2015. No centre-level data were available on centres invited each year apart from the total number of centres that were contacted by email. The questionnaire changed slightly from year to year and new variables were created with a consolidated coding frame, e.g. YFVC typology. Open-ended questions about other reason for e.g. wastage were coded to take into account additional categories. The cross-walk tables and coding frames for these additional items are provided in the Annexes. Data from military centres collected in 2015 were excluded from the analysis. The online survey was designed and implemented using SurveyGizmo (SurveyGizmo, Boulder, Colorado, USA). Data analyses were carried out using Stata 14.1 (StataCorp, College Station, Texas, USA). An extract of the Medicines and Healthcare product Regulatory Agency (MHRA) Yellow Card database was obtained to evaluate the safety data captured by the Annual Returns Survey.

Table 1 Responses and response rates of the Yellow Fever Vaccination Centres (YFVC) Annual Returns survey 2013-2015.

Year	Invites	Responses*	Duplicates*	Response rate%
2013	3,726	2,649	211	71.1
2014	3,595	2,868	131	79.8
2015	3,463	2,781	157	80.3

*) responses de-duplicated keeping latest complete response only

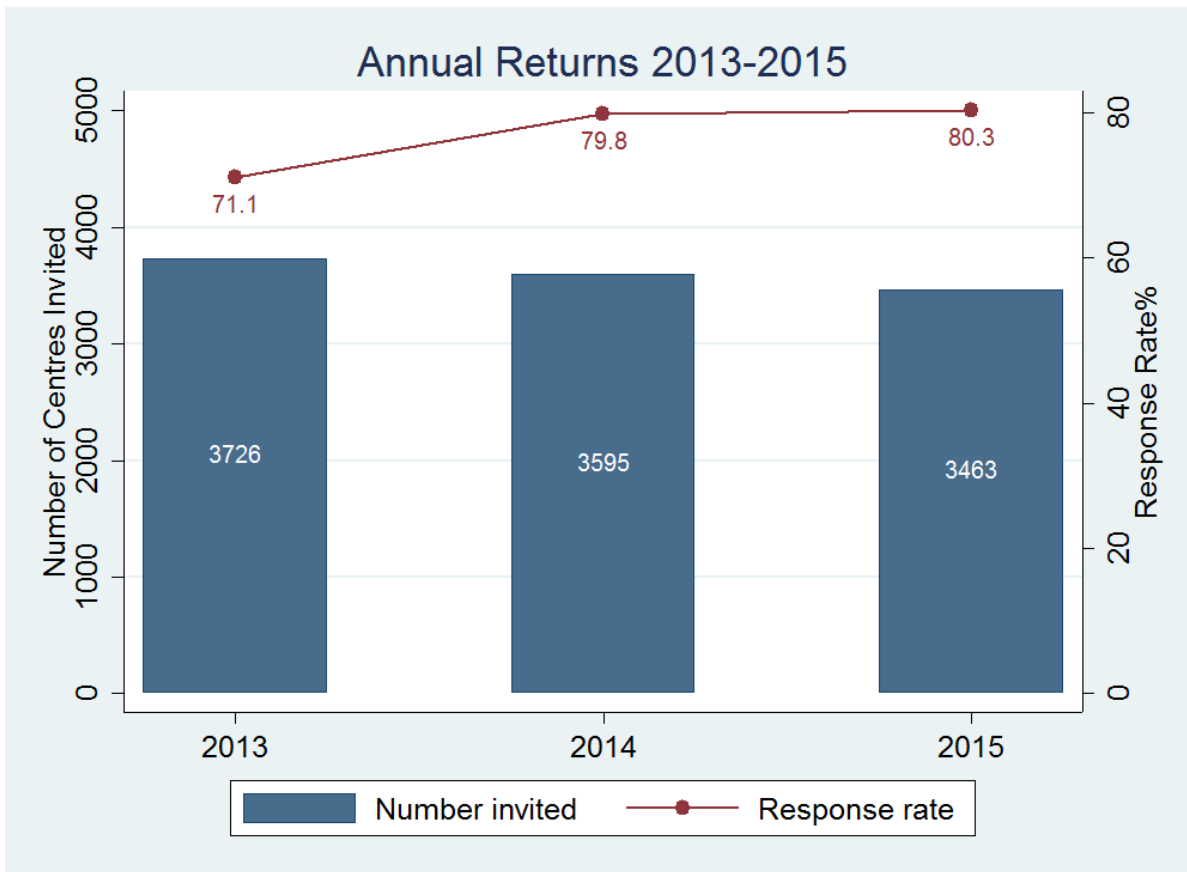


Figure 1 Number of yellow fever vaccination centres (YFVC) invited and response rate by year.

RESULTS

YELLOW FEVER VACCINES ADMINISTERED

Non-responding centres were assumed to have the same prescribing pattern as responding centres in the analyses. The total number of reported vaccinations administered fell from 163,788 in 2013 to 135,650 in 2014 and to 130,349 in 2015 (Table 2; Figure 2). The fall in the estimated numbers was 17% between 2013 and 2014 and 12% between 2013 and 2015. The number of vaccines per centre fell from 44 in 2013 to 38 in 2014 and 2015 (Table 2). The number of vaccines administered per centre varied from none to a maximum of 2,751 in 2013, 2,566 in 2014, and 1,513 in 2015.

Table 2 Number of yellow fever vaccines administered in England, Wales, and Northern Ireland 2013-2015.

Year	Vaccines administered	Vaccines administered per centre		Estimated number of vaccines administered*
		Mean	(Min;Max)	
2013	116,445	44	(0;2,751)	163,788
2014	108,218	38	(0;2,566)	135,650
2015	105,194	38	(0;1,513)	130,349

*) Assuming non-responding centres had the same prescribing pattern as responding centres.

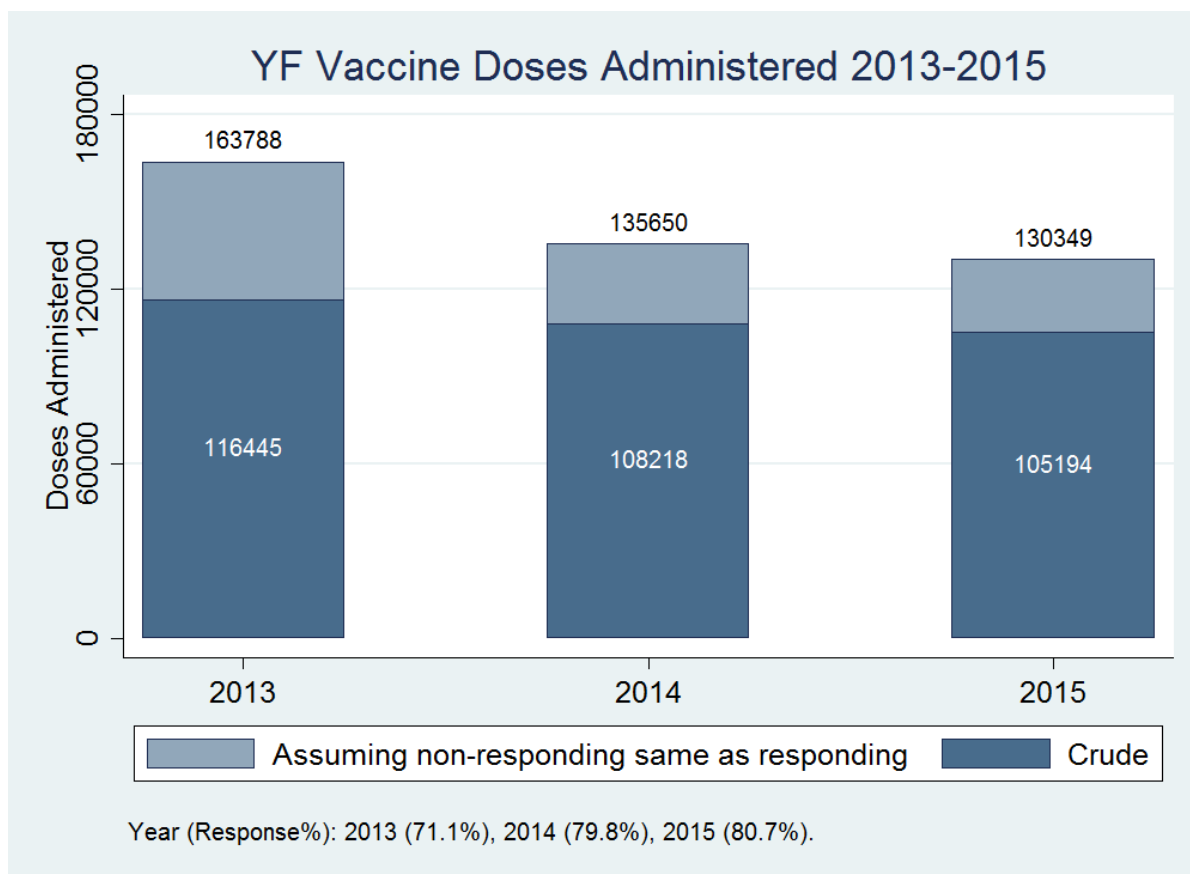


Figure 2 Estimated number of yellow fever vaccines administered by year.

Table 3 Numbers of yellow fever vaccine doses administered by reason in 2013-2015.

Year	Vaccines administered	Booster doses administered out of all administered		Booster doses administered to comply with IHR out of all boosters		Booster doses administered for continued protection out of all boosters		Booster doses administered due to traveller insistence out of all boosters	
	N	N	%	N	%	N	%	N	%
2013	116,445	8,152	7.0						
2014	108,218	7,222	6.7	6,487	89.8	2,489	34.5	280	3.9
2015	105,194	8,001	7.6	5,519	69.0	2,472	30.9	425	5.3

The questions on vaccine doses administered were nested such that total vaccine doses administered should be equal to or greater than the total number of booster doses administered which in turn should be equal to or greater than the sub-questions about reasons for giving boosters (compliance with International Health Regulations (IHR), continued protection, or traveller insistence). A small number of centres reported numbers that were inconsistent, i.e. the number of boosters exceeded the overall number of vaccines administered or at least one of the numbers of boosters by reason exceeded the overall number of boosters. A total number of 384 (4.6%) out of 8,298 centres had inconsistent numbers. The data are presented *with* (Table 3) and *without* these outliers for sensitivity (Table 4). A small number of centres in 2013 in particular had inconsistent and outlying data on the number of boosters, so that the proportion of booster doses out of all doses fell from 7.0% to 1.8% once these outliers were removed (Table 4).

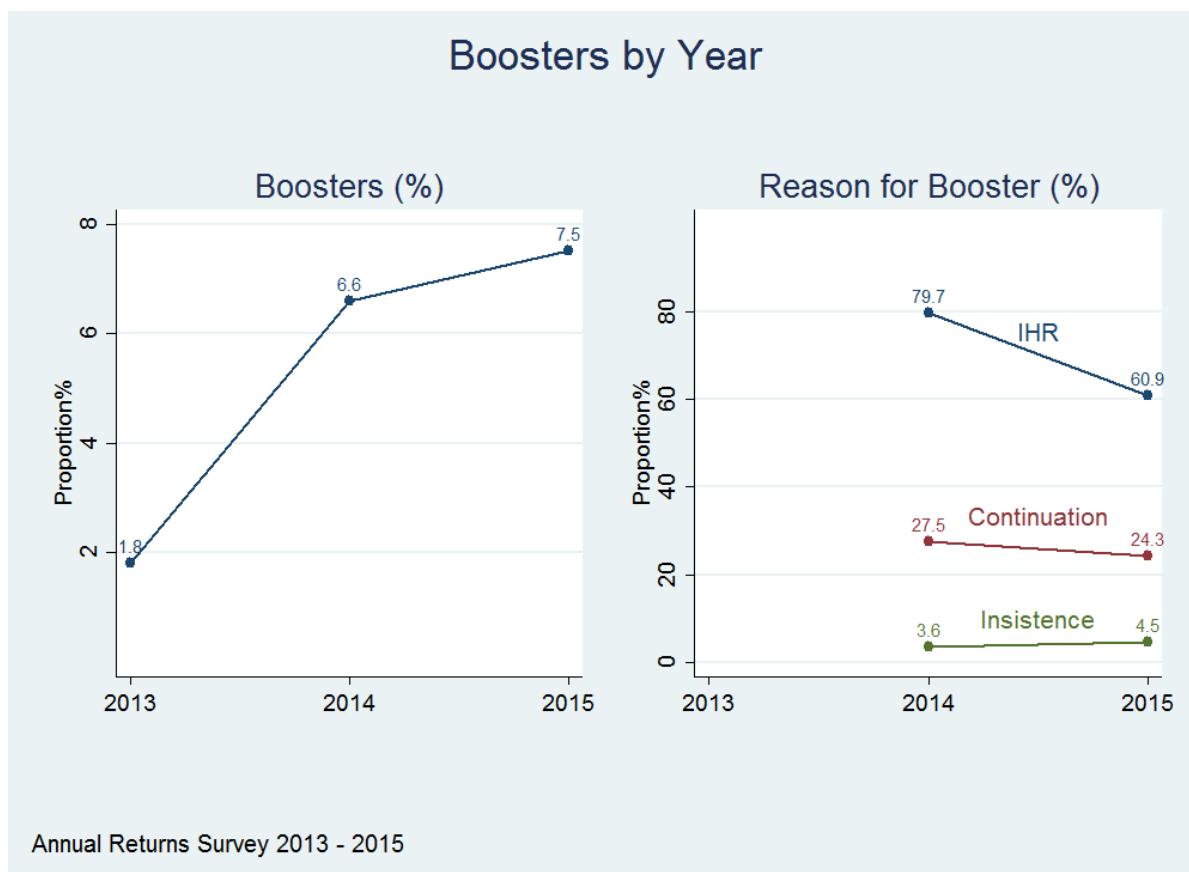


Figure 3 Booster doses: proportion of all vaccines administered and reasons. Outliers removed.

NUMBERS OF AND REASONS FOR ADMINISTERING YELLOW FEVER BOOSTER DOSES

The proportion of booster doses of all administered doses increased from 1.8% in 2013 to 6.6% in 2014 and 7.5% in 2015 (Table 4; outliers removed). The proportion of booster doses administered in compliance with IHR fell from 79.7% in 2014 to 60.9% in 2015. The proportion of doses administered for continued protection decreased slightly from 27.5% in 2014 to 24.3% in 2015. The proportion of doses administered at the insistence of the traveller increased slightly from 3.6% in 2014 to 4.5% in 2015.

Table 4 Numbers of yellow fever vaccine doses administered by reason in 2013-2015 - outliers removed*.

Year	Vaccines administered	Booster doses administered out of all administered		Booster doses administered to comply with IHR out of all boosters		Booster doses administered for continued protection out of all boosters		Booster doses administered due to traveller insistence out of all boosters	
	N	N	%	N	%	N	%	N	%
2013	116,031	2,111	1.8						
2014	106,620	7,003	6.6	5,578	79.7	1,928	27.5	249	3.6
2015	103,543	7,727	7.5	4,702	60.9	1,880	24.3	348	4.5

*) Excluding data from 384 centres (4.6%) with inconsistent reporting on numbers of vaccine doses.

YELLOW FEVER VACCINATION CENTRES TYPES

The question about centre type changed each year. The trend in centre type is shown as changes in estimated numbers assuming non-responding centres had similar prescribing patterns to responding centres (Table 5; Figure 4). The number of centres declined by 5% between 2015 and 2013 (Table 5). The biggest decline (-46%) was seen in occupational health departments from an estimated 142 centres in 2013 to 77 in 2015. The proportion of private GP practices fell by 38% from an estimated 309 practices in 2013 to 192 practices in

2015. The proportion of pharmacies increased the most (725%) from an estimated 56 in 2013 to 462 in 2015. Travel clinics went up by 84% from an estimated 135 clinics in 2013 to 249 clinics in 2015. The overall trend in the estimated number of centres by type: travel clinics increased between 2013 and 2014, pharmacies increased year on year, both occupational health departments and GP practices (private and public) declined year on year. The size distribution of centres in terms of the number of vaccines administered by type is shown for 2015 as a [violin plot](#) in Figure 5.

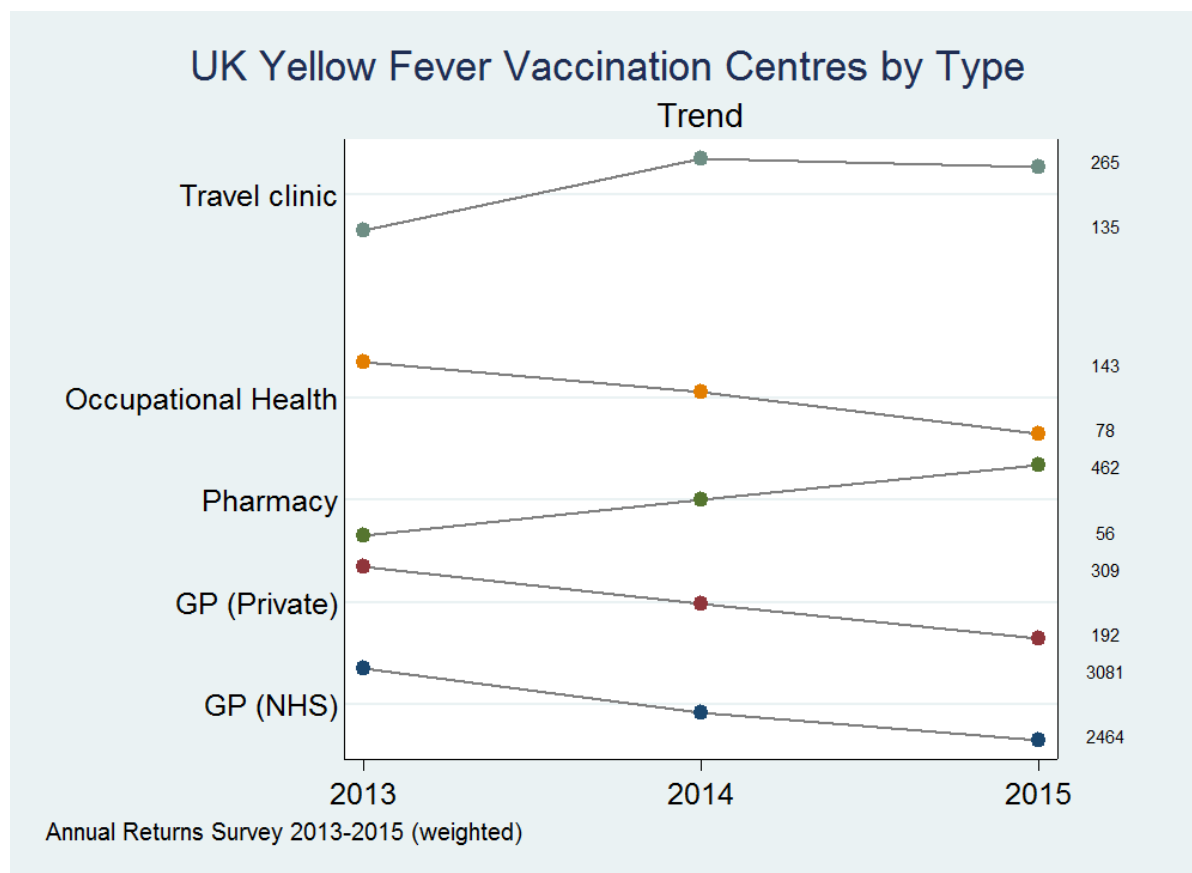


Figure 4 UK Yellow fever vaccination centres by type 2013-2015.

Table 5 Yellow fever vaccination centres by type 2013-2015.

Type of centre	2013	2014	2015	2013*	2014*	2015*	Difference % 2014-2013*	Difference % 2015-2013*
GP (NHS)	2,191	2,156	1,989	3,081	2,702	2,464	-12	-20
GP (Private)	220	198	155	309	248	192	-20	-38
Pharmacy	40	209	373	56	262	462	366	725
Occupational Health	102	93	63	143	117	78	-18	-46
Travel clinic	96	212	201	135	265	249	96	84
Total	2,649	2,868	2,781	3,726	3,595	3,446	-4	-5

*) assuming non-responding centres were no different from responding centres.

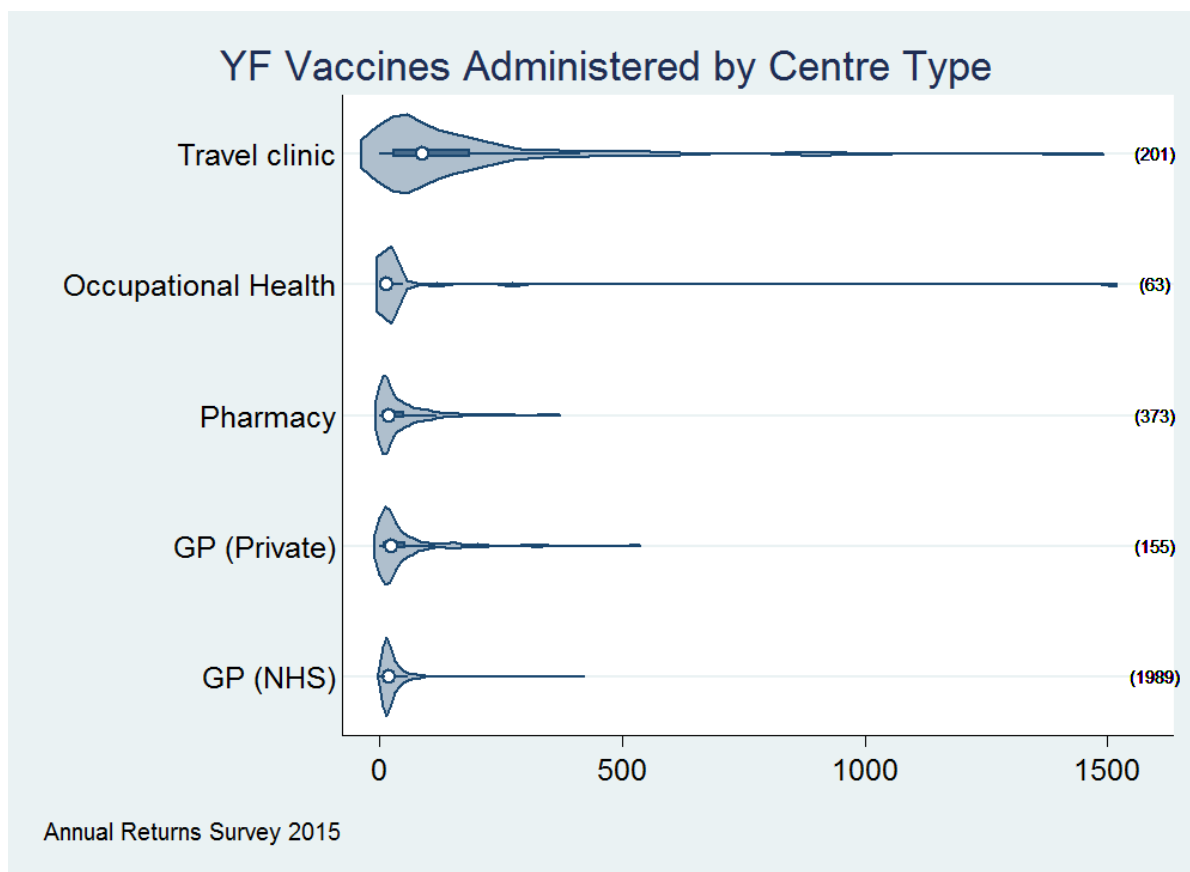


Figure 5 Yellow fever vaccines administered by centre type in 2015 (violin plot; number of centres shown in brackets).

YELLOW FEVER VACCINATION CENTRE DESIGNATION STATUS

The majority of centres had been designated for a year or more (Table 6). The number of newly designated centres was highest in 2014. The category for de-designated status was introduced in 2014. More centres had this status in 2014 than in 2015.

Table 6 Yellow fever vaccination centre designation status 2013-2015.

Designation status	2013	2014	2015	2013*	2014*	2015*
Designated <1 year	72	200	164	101	251	203
Designated ≥1 year	2,577	2,532	2,596	3,625	3,174	3,217
De-designated status		136	21		170	26
Total	2,649	2,868	2,781	3,726	3,595	3,446

*) Assuming non-responding centres were no different from responding centres (rounded figures).

YELLOW FEVER VACCINATIONS: SERIOUS ADVERSE EVENTS

The question on the number of serious adverse events had three categories: none, 1-5, or >5. If a centre responded ">5" the respondent was instructed to email the UK yellow fever vaccination programme administration with the details. A total of seven centres ticked this category although no further data were received by 24 May 2016 for the 2015 survey and any data from 2014 were either lost or never received. A number of responses were inconsistent in the way that despite "None" was selected in response to the initial question details were subsequently given about events. A total of seven, 14 and 13 serious adverse events were captured in 2013, 2014, and 2015, respectively (Table 7).

Table 7 Number of yellow fever vaccination serious adverse events 2013-2015

Number of serious adverse events reported to MHRA	2013	2014	2015
1-5	4	2	2
>5		3	4
None (but details of 1 case given)	1	12	9
None (but details of 3 cases given)			1
None/1-5 cases mentioned (no details given)	1		
None	2,643	2,851	2,836
Total centres	2,649	2,868	2,852
Number with case detail*	7	14	13

*) Excluding where >5 cases were reported and data were not subsequently received as per instructions in questionnaire or data were lost.

The characteristics of serious adverse events were only sparsely reported and are shown in Table 8.

Table 8 Characteristics of reported serious adverse events in connection with yellow fever vaccinations 2013-2015*

Characteristics	Categories	2013	2014	2015
Age group	6 to <9 months		1	
	9 months to 9 years		1	
	10-19 years			1
	20-29 years		1	1
	30-39 years	1		
	40-49 years			
	50-59 years			
	60+ years	1	2	2
Sex	Female	3	1	1
	Male	2	2	4
Serious adverse event type	Anaphylaxis	1		1
	YEL-AND	1	1	2
	YEL-AVD			
Status of serious adverse event	Suspected	1	2	4
	Confirmed		1	

*) Case details were only sparsely reported.

The safety data captured by the Annual Returns Survey 2013-2015 were compared with an extract of the MHRA Yellow Card database, which contained 98 case reports with 457 reactions including a fatal case (Table 9). The proportion of case reports captured by the survey was 39% (shortfall: 61%). For details about age this proportion was 13%, for sex 15%, and for any details about the reaction it was 7%. A total of two anaphylaxis cases and four cases of Yellow Fever Vaccine Associated Neurotropic Disease (YEL-AND) were captured by the survey. Further analysis of the data would be required to establish the degree to which the survey captures the most serious adverse events. Possible reasons for the shortfall (61%) in capturing serious adverse events in the Annual Returns Survey were;

1. Unit non-response
 - a. Centre contact details out of date
 - b. Email request lost

- c. Centre refusal
- 2. Item non-response
 - a. Centre refused to answer questions about serious adverse events
 - b. Centre respondent misunderstood question or had problems navigating the questionnaire
 - c. Data loss
- 3. Questionnaire design
 - a. Centres with >5 serious adverse events to report failed to email the details to the programme administration (as per instructions in questionnaire)
 - b. Data never received by email or lost
- 4. Bias due to event being reported by a different organisation to the one prescribing, e.g. a traveller vaccinated in private sector may present with symptoms of an adverse event at an NHS GP practice or a hospital accident and emergency department, which reports the event to MHRA. In that case the prescribing organisation would not have been the one reporting the event.

Table 9 Serious adverse events captured by Annual Returns Survey 2013-2015 compared to MHRA's Yellow Card database.

	MHRA	MHRA*	Annual Returns Survey	
	2013 to 5 May 2016	2013-2015	2013-2015	
	N	N	N	%
Case reports with any details at all	98	88	34	39
Case reports with any details - Age			11	13
Case reports with any details - Sex			13	15
Case reports with any details - Any reaction			6	7

*) 89.7% of reference time period.

YELLOW FEVER VACCINATION ERRORS

A total of 13 and 15 vaccination errors were reported in 2014 and 2015, respectively (Table 10). In a single case the vaccine had been administered despite contra-indication. In four cases the vaccine had been given off-label. In nine cases only the diluent was administered.

Table 10 Yellow fever vaccination errors reported (multi-choice) 2014-2015

Vaccination error type	2014	2015
Given when contra-indicated		1
Given off-label	1	3
Diluent only administered	4	5*
Other	8	6
Total	13	15

YELLOW FEVER VACCINE WASTAGE

The most commonly reported reason for vaccine wastage was cold chain breakdown followed by vaccine out of date and product fault (Table 11).

Table 11 Reasons for yellow fever vaccine wastage (multi-choice) 2013-2015

Reasons for wastage	2013	2014	2015
Cold chain breakdown	83	83	94
Vaccine out of date	57	38	56
Product fault	23	26	37
Other	103	127	121

Open-ended responses to other reasons for wastage were coded and the results are shown in Table 12. Notably, reports of problems with multi-dose vials peaked in 2013 (N=17) and 2014 (N=27), where batches of multi-dose vials were distributed during a period of vaccine shortage in the UK.

Table 12 Other reasons for yellow fever vaccine wastage 2013-2015. Open-ended category coded (see Table 11)

Other reasons for wastage	2013	2014	2015
Cold chain breakdown	24	16	22
Vaccination out of date	1	3	
Other	22	34	38
Dropped vial	11	15	17
Syringe fault	7	18	17
Patient refused	15	8	21
Patient unsuitable	5	4	7
Centre deregistration		2	3
Multi-dose vial problem	17	27	2

FINDINGS

DETERMINE COMPLIANCE WITH SURVEY

1. The number of registered centres invited to take part in the Annual Returns Survey fell from 3,726 in 2013 to 3,595 in 2014 and 3,463 in 2015.
2. The response rate for the same years went up from 71.1% in 2013 to 79.8% in 2014 and 80.3% in 2015.
3. Non-responding centres were assumed to have similar prescribing patterns to responding centres.

IDENTIFY ANY CHANGES IN THE TYPE OF YELLOW FEVER VACCINATION CENTRES

4. The number of centres declined by 5% between 2015 and 2013.
5. The biggest decline (-46%) was seen in occupational health departments from an estimated 142 centres in 2013 to 77 in 2015.
6. The proportion of private GP practices fell by 38% from an estimated 309 practices in 2013 to 192 practices in 2015.
7. The proportion of pharmacies increased the most (725%) from an estimated 56 in 2013 to 462 in 2015.
8. Travel clinics went up by 84% from an estimated 135 clinics in 2013 to 249 clinics in 2015.
9. The overall trend in the estimated number of centres by type: travel clinics increased between 2013 and 2014, pharmacies increased year on year, both occupational health departments and GP practices (private and public) declined year on year.

QUANTIFY YELLOW FEVER VACCINES ADMINISTERED

10. The total number of reported vaccinations administered fell from 163,788 in 2013 to 135,650 in 2014 and 130,349 in 2015. The fall in the estimated numbers was 17% between 2013 and 2014 and 12% between 2013 and 2015.
11. The mean number of vaccines administered per centre fell from 44 in 2013 to 38 in 2014 and 2015.
12. The number of vaccines administered per centre varied from none to a maximum of 2,751 in 2013, 2,566 in 2014, and 1,513 in 2015.

IMPACT OF WHO 2013 GUIDANCE REGARDING YELLOW FEVER VACCINE BOOSTER DOSES

13. The proportion of booster doses of all administered doses increased from 1.8% in 2013 to 6.6% in 2014 and 7.5% in 2015 (outliers removed).
14. The proportion of booster doses administered in to comply with IHR fell from 79.7% in 2014 to 60.9% in 2015.
15. The proportion of doses administered for continued protection decreased slightly from 27.5% in 2014 to 24.3% in 2015.
16. The proportion of doses administered at the insistence of the traveller increased slightly from 3.6% in 2014 to 4.5% in 2015.

IMPACT OF YELLOW FEVER VACCINE SHORTAGE IN THE UK IN 2013-2015

17. The number of centres declined by 4% between 2013 and 2014, and by 5% between 2013 and 2015.
18. The number of vaccines administered declined by 17% between 2013 and 2014, and by 12% between 2013 and 2015.

19. Mentions of vaccine wastage associated with the use of multi-dose vials peaked in 2013 (N=17) and 2014 (N=27), where batches of multi-dose vials were distributed during a period of vaccine shortage in the UK.

DETERMINE THE NUMBER AND NATURE OF REPORTED ADVERSE EVENTS

20. The proportion of serious adverse event cases captured by the survey relative to MHRA's Yellow Card database was 39% (shortfall: 61%).
21. For details about age this proportion was 13%, for sex 15%, and for details about any reactions 7%.
22. A total of two anaphylaxis cases and four cases of YEL-AND were captured by the survey.
23. Further analysis of the data would be required to establish the degree to which the survey captures the most serious adverse events reported to the Yellow Card database.
24. A total of 13 and 15 vaccination errors were reported in 2014 and 2015, respectively. In a single case the vaccine had been administered despite contra-indication. In four cases the vaccine had been given off-label. In nine cases only the diluent was administered.
25. Possible reasons for the shortfall (61%) in capturing serious adverse events in the Annual Returns Survey were;
 - a. Unit non-response
 - i. Centre contact details out of date
 - ii. Email request lost
 - iii. Centre refusal
 - b. Item non-response
 - i. Centre refused to answer questions about serious adverse events
 - ii. Centre respondent misunderstood question or had problems navigating the questionnaire
 - iii. Data loss
 - c. Questionnaire design
 - i. Centres with >5 serious adverse events to report failed to email the details to the programme administration (as per instructions in questionnaire)
 - ii. Data never received by email or lost
 - d. Bias due to event being reported by a different organisation to the one prescribing, e.g. a traveller vaccinated in private sector may present with symptoms of an adverse event at an NHS GP practice or a hospital accident and emergency department, which reports the event to MHRA. In that case the prescribing organisation would not have been the one reporting the event.

ANNEXE 1 CODING FRAMES FOR CONSOLIDATED AND CODED VARIABLES

YELLOW FEVER VACCINATION CENTRE TYPOLOGY

The question about centre type changed each year and the cross-walk table and consolidated coding frame are shown below.

2013	2014	2015	centretype	label
General National Health Service (NHS) Practice (contracted to provide general medical services)			1	GP (NHS)
	National Health Service (NHS) General Practice (contracted to provide general medical services)		1	GP (NHS)
		General Practice - National Health Service (NHS)	1	GP (NHS)
Private Practice (contracted to provide general medical services)			2	GP (Private)
	Private General Practice		2	GP (Private)
		General Practice - Private	2	GP (Private)
Pharmacy	Pharmacy		3	Pharmacy
		Pharmacy - NHS	3	Pharmacy
		Pharmacy - Private	3	Pharmacy
Occupational Health Department of an Organisation Centre providing Occupational Health Services	Occupational Health Department of an Organisation	Occupational Health Department of an Organisation	4	Occupational Health Department
			4	Occupational Health Department
	Occupational Health Services Provider		4	Occupational Health Department
		Occupational Health Department of a Service Provider	4	Occupational Health Department
Centre open to the Public (managed by a Health Authority/NHS Trust/Individual/Organisation) Hospital			5	Travel clinic
			5	Travel clinic
	Hospital Travel Clinic		5	Travel clinic
		Travel Clinic open to the Public (managed by a Health Authority/NHS Trust)	5	Travel clinic
	Private Travel Clinic		5	Travel clinic
		Travel Clinic - NHS (managed by a Health Authority / NHS Trust)	5	Travel clinic
		Travel Clinic - Private	5	Travel clinic

YELLOW FEVER VACCINATION CENTRE DESIGNATION STATUS

The option for centres to be de-designated was only carried 2014-2015 and the question wording varied slightly year on year for other categories. The cross-walk table and consolidated coding frame are shown below.

2013	2014	2015	desighistory	label
We have been designated for less than one year (this is the annual return for only part of 2013).			1	<1 year
	We have been designated for less than one year (this is the annual return for only part of 2014)		1	<1 year
		We have been designated for less than one year (this is the Annual Return for only part of 2015)	1	<1 year
We have been designated for over one year (this is the annual return for the whole AR term).			2	>1 year
	We have been designated for over one year (this is the annual return for 2014).		2	>1 year
		We have been designated for over one year (this is the Annual Return for 2015).	2	>1 year
	We are currently not a yellow fever vaccination centre (this annual return is for part of or the whole of 2014).		3	De-designated status
		We are currently not a YFVC (this Annual Return is for part of or the whole of 2015).	3	De-designated status

CODING FRAME FOR OTHER REASON FOR VACCINE WASTAGE

The reasons for wastage were captured by individual questions (1-4) and an open-ended question about other reasons for wastage was coded to the coding frame below.

Code	Label
1	Cold chain breakdown
2	Vaccination went out of date
3	Product fault
4	Other
11	Dropped vial
12	Syringe fault
13	Patient refused
14	Patient unsuitable
15	Centre deregistration
16	Multi-dose vial problem

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