Stimulating Antibiotic R&D

An analysis of key factors – R&D success, R&D duration and the impact of generic launch

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Executive Summary

A focus of the Review on Antimicrobial Resistance is analysis of different incentives to stimulate new antibacterial development. The Review requested that IMS estimate some of the key parameters that are to be used in the assessment of such incentives. These include antibiotic R&D success rates and development phase duration as well as the impact of generic launch on both volume and value. IMS estimates are compared to those put forward by the Eastern Research Group (ERG) in 2014. Estimates of antibiotic R&D success rates and phase duration were derived from analysis of IMS Health's R&D Focus database. Estimates of generic impact on antibiotic value and volume sales were derived from IMS' audits in 7 major markets – France, Germany, Italy, Japan, Spain, UK and USA. ERG estimates were based primarily on literature review.

The observed success rate for antibiotic R&D in the IMS R&D Focus database across all phases (preclinical to registration) was approximately one half lower than that proposed in the ERG model (1.5% versus 3.3%). Success rates in Phase II and III are however noticeably higher than those proposed in the ERG model. It should be noted however that the clinical phases in this study were dominated by antibiotics from existing classes, so success rates may therefore be higher. On the other hand, the observed rate for clinical phases reported in this study is similar to that observed in a separate study also focusing specifically on systemic anti-infectives in development between 1993 and 2004 (16.1% versus 15.6%).

The observed duration of the clinical phases was somewhat longer than that proposed in the ERG model whilst the observed duration of the preclinical phase was somewhat shorter. Differences in preclinical phase length may be due to classification or reporting differences.

The impact of generic launch on antibiotic revenues suggests that loss of revenue is deeper and longer for antibiotics than was anticipated by the ERG model. The median loss of revenue across all countries combined after 12 months was 66%, at 24 months 77% and at 36 months 81%. This compares to a figure of 50% (range 25-75%) given in the ERG model for USA only. It should be noted however, first that these IMS estimates hide considerable variability between countries and second that the declines may be even steeper owing to discounting practices not able to be seen in the IMS data.

Analysis of the impact of generic launch on volumes focused on two particular cases - a parenteral carbapenem and an oral fluoroquinolone. Interrupted time series analysis on seasonally adjusted data indicated that the impact of generic launch varied in both direction and significance across countries. In short no consistent effect could be detected.

Introduction

The Review on Antimicrobial Resistance is to recommend a series of actions designed to tackle the growing threat from antibiotic resistance. The first report estimated that if antimicrobial resistance (AMR) continues to rise, an additional 10 million people would be expected to die in 2050, and the world would see a reduction in Gross Domestic Product of between 2% and 3.5%.[1] The second report proposed a series of initiatives to address the problem of chronic under-investment in both the financial and human capital needed to tackle AMR. [2]

Current work is focused on an analysis of different incentives to stimulate new antibacterial development. An analytical framework to examine the effect of different policy alternatives was commissioned by the US Department of Health and Human Services from the Eastern Research Group (ERG) in 2014.[3] That ERG framework builds in a number of attributes including those relating to total Research and Development (R&D) cost, R&D success rates, time in development, distribution, post-marketing surveillance, market penetration and market value. The ERG framework was populated using a variety of information sources including secondary literature describing R&D success rates and the duration of development across a mix of therapy classes, and data from IMS Health (IMS) relating to the sale of particular antibiotics in the USA.

This paper helps to update some of the information used to populate the ERG model. The Review on Antimicrobial Resistance requested that IMS estimate:

- Success rates by development phase, focusing on antibiotics alone.
- Duration of the different development phases, again focusing on antibiotics alone.
- The impact of generics on antibiotic sales and volume across the 7 major high income countries (France, Germany, Italy, Japan, Spain, United Kingdom, USA).

Data sources and methods differ depending on the area. These are therefore addressed separately below.

Materials and Methods: R&D

Data relating to projects in research and development were taken from IMS' R&D Focus database. The main sources of information for R&D Focus are company press releases, company interviews and websites, and scientific conferences. R&D Focus lists the product name, the "latest news" about the product, whether or not the product has been discontinued or is still in active development and its mode of action. Projects are classified according to their relevant therapy class (European Pharmaceutical Market Research Association Anatomical Therapy Codes (EphMRA ATC). Antibiotic projects were extracted using the EphMRA ATC codes, J1 (Systemic Antibiotics), J8 (anaerobicides), G1A (Trichomonacides) and G4A (Urinary anti-antifectives). The latest phase of development is generally recorded separately in R&D Focus but for some records, this is shown only as "discontinued" or "suspended". In these cases, the latest phase as recorded in the latest news was used. Projects for which no news is heard for more than 36 months are deemed to be discontinued in the database. The duration of development was derived from the dates shown in the latest news.

The progress of projects in active development in December 2002 was tracked through to March 2015, a maximum follow up period of more than 12 years. Of the 246 projects identified, 108 were excluded, 47 because although the product was in active development it had already been launched, 38 because the project was described as a drug delivery system, a technology or development programme rather than an actual compound, 18 because later information showed that the antibiotic or compound was not being developed as a systemic antibiotic, 3 because the date of discontinuation was unclear and thus potentially prior to December 2002, 1 because of conflicting phase information and 1 because the project could not be linked through to the 2015 database. As a result, 138 projects are included in this analysis. Of these 138

projects, 107 were in the preclinical phase ("Preclinical") in December 2002, 12 in Phase I, 8 in Phase II, 7 in Phase III and 4 in Pre-registration. As might be expected the clinical phases were dominated by what are now relatively well known classes of antibiotics, including 10 quinolones, 6 carbapenems, 3 glycopeptides and 3 cephalosporins. In some cases the date of the latest news (and phase) was the same in both the December 2002 database and the March 2015 database (i.e. there had been no update). These cases were excluded from calculations of phase duration. Overall success rates were calculated by multiplying out the success rates of each phase. For example if 100 molecules enter the preclinical phase, and the preclinical success rate is 35%, then 35 molecules enter Phase 1. If the success rate in Phase 1 is 33%, then 11.55 molecules enter Phase 2 (35*33%) and so on.

Materials and Methods: Generic launch

Data reflecting the value and volume of antibiotic sales and the penetration of generics were derived from IMS data collected from both hospital and retail sectors in France, Germany, Italy, Japan, Spain, UK and USA. These data will contain a mix of pharmacy procurement and dispensing data depending on the setting and time period. Values and volumes were extracted for systemic antibiotics linked to the EphMRA ATCs J1, J8, G1A and G4A, and organised according to antibiotic class.

Molecules and pharmaceutical dosage forms were classified into those that were "protected", those that were "no longer protected" and those that were "never protected". Generics fall into the "never protected" category whilst products that have lost protection are "no longer protected". Protection takes into account known molecule product patents, delivery device patents, composition patents, process patents, Method of Use patents, Supplementary Protection Certificates, Certificats Complementaire de Protection, marketing exclusivity, data exclusivity, orphan drug exclusivity, paediatric indication extension and known ongoing litigation. Protection is country-specific and varies by month.

Volumes were converted to the WHO Defined Daily Dose (DDD)[4]. In the event that no DDD had been assigned to a combination product then where possible the amount of each of the antibiotics within the compound was calculated and the DDD for each antibiotic was used. In the event that no DDD had been assigned to a product that contained only one active ingredient, then the recommended daily dose as found on the manufacturer's product information or in other literature was used.

Values were converted from local currency to $US using the average exchange rate for the month of sale. Values were expressed as $US per DDD at estimated ex-manufacturer price. IMS will tend to over-estimate actual ex-manufacturer price. This is because some types of discounts, notably off-invoice discounts or rebates paid to payors are not able to be captured.

The impact of generic launch on value was expressed as the absolute percentage decline in revenues of the no longer protected product at 12, 24 and 36 months following the loss of protection, this being relative to the revenues achieved in the month prior to generic launch. Two different results are shown – first the median value across all countries combined, and second the median of the individual medians calculated for each country. All antibiotics (molecules and dosage form) whose protection expired between 2008 and 2012 were identified and included in this study. This list differs by country given that protection varies by country.

The impact of generic launch on volume was investigated using two different examples – the effect of loss of protection for meropenem (a carbapenem antibiotic) on the volume sales of all carbapenems, and the effect of the loss of protection for oral levofloxacin (a quinolone antibiotic) on the sales of all quinolones. Reasons for choosing these two examples include (a) loss of protection occurred in all 7 countries within the time period of the study, (b) loss of protection occurred midway through the time period in most countries allowing pre-existing

trends to be seen with adequate follow up post loss of protection, and (c) oral quinolones are used in both community and hospital care settings whilst carbapenems will be used almost entirely in a hospital care setting. Data from Japan was excluded as loss of protection occurred too early in the time series. Data relating to the carbapenems in Spain were also excluded for the same reason. Data are expressed as DDDs per 1000 population.[5] The effect of loss of protection was analysed using Interrupted Time Series analysis on seasonally adjusted data. Seasonal decomposition was carried out using IBM SPSS Statistics 20. The Interrupted Time Series was carried out using an ARIMA (Autoregressive Integrated Moving Average) model in IBM SPSS Statistics 20. Interrupted Time Series Analysis estimates "the effect of the intervention whilst taking account of time trend and autocorrelation among the observations. Estimates for regression coefficients corresponding to two standardised effect sizes are obtained: a change in level (also called 'step change') and a change in trend before and after the intervention" [6]. A change in level is "defined as the difference between the observed level at the first intervention time point and that predicted by the pre-intervention time trend, and a change in trend is defined as the difference between post- and pre-intervention slopes."[6] The model used here allows the combined effect of the intervention on both trend and level to be quantified at a particular time point of interest.[6] In this study, the change in the number of DDDs used per 1000 population associated with the intervention at 12 months post intervention was calculated. 12 months post intervention was chosen as the time point of interest so as to ensure that if effects could be detected then those effects would be seen as being persistent over time. Serial autocorrelation was controlled for using an autoregressive error model. Step-wise elimination of autoregressive parameters with $p>0.05$ was carried out.

Results: R&D

- **SUCCESS RATES BY PHASE**

The observed success rates for antibiotics in development in December 2002 are compared with those predicted in the ERG model in Table 1 below. The observed rates for the Preclinical phase, Phase II and Phase III are outside of the bounds used in the ERG model. Overall success rates are also therefore different. The observed success rate for all clinical phases combined is in fact almost double that used in the ERG model. In contrast the observed rate for clinical phases shown here is similar to that observed for systemic anti-infectives in development between 1993 and 2004 (16.1% versus 15.6%).[7]

The lower success rate for the preclinical phase may be due to differences of classification. In reports of R&D it can sometimes be difficult to distinguish between discovery and preclinical phases. The observed results may therefore include projects that with more information might have been classed as within the discovery phase, so distorting the success rates. On the other hand preclinical failures may be less likely to be publicised by companies and so not reach development databases such as R&D Focus.

Phase	ERG Rate	Observed rate
Preclinical	**35.2% (17.5-69.0%)**	**9.3%**
Phase I	**33.0% (25.0%-83.7%)**	**33.3%**
Phase II	**50.0% (34.0% - 74.0%)**	**75.0%**
Phase III	**67.0% (31.4%-67.0%)**	**85.7%**
NDA/BLA (Pre-registration)	**85.0% (83.0%-99.0%)**	**75%**
Overall (Preclinical+)	**3.3%**	**1.5%**
Overall (Clinical+)	**9.4%**	**16.1%**

Table 1: Comparison of the observed success rates for antibiotics in development as of December 2002 with those used in the ERG model

- **PHASE DURATION**

To estimate phase duration, projects were first divided into two groups. The first group consisted of those reaching pre-registration or launch. These might be considered as "successful". The second group consisted of those that failed to move out of their current phase as of December 2002 or moved just one phase. These projects might be regarded as having "failed", for clinical or strategic reasons. Projects were divided into these two groups in order to allow for the fact that successful projects may move through the development phases rather faster than those that eventually fail, or perhaps for the fact that notification of failure may be rather slower to emerge than notification of success. In both groups duration was calculated from the difference in the date of the latest news. Projects where the date of the latest news was the same in both the 2002 and 2015 database were excluded as no phase duration could be calculated. Table 2 gives the results for the projects reaching pre-registration or marketed status, Table 3 the results for the projects that failed to progress or only progressed to the next phase.

	Time to preregistration or launch (months, median used where n >1)	
From \ To	Preregistration	Marketed
Preclinical	153.2 (n=1)	99.3 (n=1)†
Phase I		111.2 (n=3)
Phase II	69.2 (n=1)	136.3 (n=1)
Phase III		65.4 (n=6)

† ERG model suggests that average time from preclinical to marketed is of the order of 120 months

Table 2: Time to preregistration or launch

	Time (months, median used where n>1)	
	Observed (R&D Focus)	ERG Model
Preclinical – Preclinical (n=4)	31.9	66.0
Preclinical – Phase I (n=1)	13.0	
Phase I – Phase I (n=7)	39.6	10.5
Phase I – Phase II (n=1)	142.5	
Phase II – Phase III (n=4)	85.2	11.0
Phase III – Preregistration (n=6)†	52.1	21.5
Pre-registration - Marketed (n=3)	13.3	9

† All successful projects in Phase III at the beginning of the study period reached Marketed status by study end. The duration of Phase III – Registration was therefore calculated by subtracting the time from Pre-registration to Marketed

Table 3: Time in development, by phase

These analyses of observed clinical phase durations would seem to be somewhat longer than those utilised in the ERG model. At the same time where the n>1, the mean and the median are relatively close indicating that there is little variation across the projects. On the other hand the duration of the observed Preclinical phase duration is smaller than that used in the ERG model.

This may be for two reasons. Some of the projects may be better classified as Discovery and the Discovery phase may be shorter than the Preclinical phase. Alternatively it appears that the latest news relating to the Preclinical phase describes work that has already begun (i.e. the latest news does not reflect the start of the preclinical phase). Nonetheless, overall the observed clinical phase durations for antibiotics in development as of December 2002 would appear to be somewhat longer than those used in the ERG model.

Results: Generic launch

- **GENERIC IMPACT (VALUE)**

The ERG model suggests that the launch of a generic, at least in the USA, leads to a decline in revenues of 50% (range 25%-50%), and that this level would remain constant over time. Analysis of the impact of generics on antibiotic revenues across the 7 high income countries included in this study indicates that loss of revenue is deeper and longer for antibiotics than was anticipated overall (Figure 1). The median loss of revenue across all countries combined after 12 months was 66%, at 24 months 77% and at 36 months 81%. This picture hides, moreover, large variation between countries as shown in Figure 5. This variation means that the relative impact of generic launch will be greater in those countries like the USA where generic penetration is swift and deep. In this respect it is important to remember that IMS audits are not able to capture off-invoice discounts or rebates. The extent of these will vary across countries but revenue decline are likely to be steeper and deeper than is shown here,

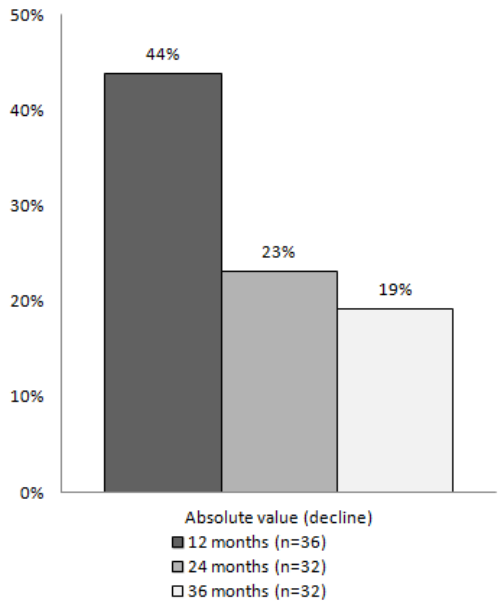


Figure 1: Median percentage of revenue remaining at 12, 24 and 36 months post generic launch (Products losing protection, 2008-2012)

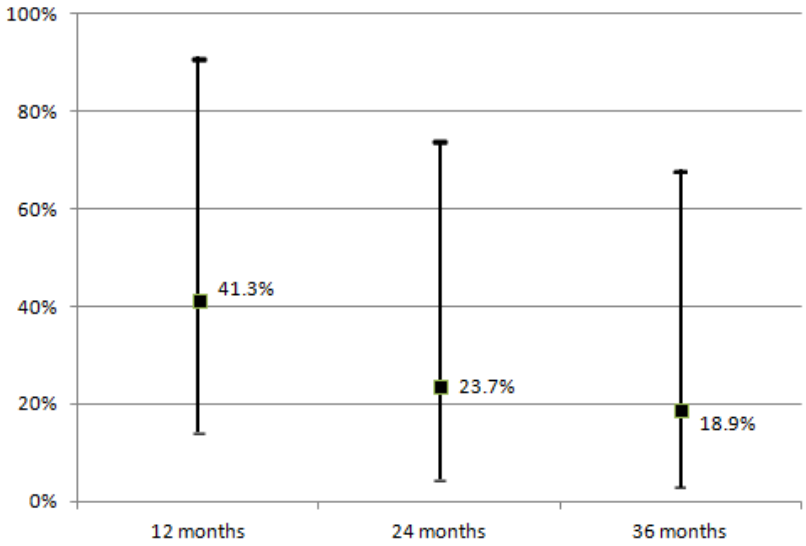


Figure 2: Variation across countries of impact of generic launch - figures represent percentage revenue remaining at 12, 24, and 36 months relative to month prior to generic launch (Values in figure represent minimum and maximum value in any country, whilst median value is the median of country median values)

- **GENERIC IMPACT (VOLUME)**

Seasonally adjusted volumes of oral quinolones and carbapenems (expressed as DDDs per 1000 population), together with the fitted model are shown in Figures 3 and 4. The blue vertical line indicates the introduction of generic formulations of meropenem and oral levofloxacin. The results of the Interrupted Times Series are shown in Tables 4 and 5 below. These tables show the combined effect of both the level change and trend change, 12 months post the launch of the generic.

	% effect	p value
France	**0.3%**	**0.81**
Germany	**-9.1%**	**<0.001**
Italy	**-2.7%**	**0.21**
UK	**4.3%**	**0.02**
US	**8.6%**	**0.001**

Table 4: The effect of the launch of a generic launch of levofloxacin on volumes of oral quinolones, 12 months post generic launch

	% effect	p value
France	**-1.1%**	**0.77**
Germany	**-3.9%**	**0.14**
Italy	**-0.7%**	**0.69**
Spain	**-16.8%**	**<0.001**
UK	**-6.5%**	**<0.001**
US	**-0.6%**	**0.87**

Table 5: The effect of the launch of a generic launch of meropenem on volumes of carbapenems, 12 months post generic launch

Tables 4 and 5 indicate that, if there is an effect on volume as a result of the launch of a generic, then that effect varies across countries:

(a) Oral quinolones: In 2 countries the effect of the launch of generic forms of levofloxacin does not reach statistical significance, in two the launch is associated with a significantly positive effect, and in one that effect is negative. The positive effect of the launch of levofloxacin post intervention can be seen in Figures 3 (D) and 3 (E) where post launch of the generic, volumes flatten out.

(b) Carbapenems: In 4 countries the effect of the launch of generic forms of meropenem does not reach statistical significance. In two countries the launch of a generic is associated with a significant effect at 12 months post intervention but in both the effect is negative. In Spain the effect of the generic launch is driven by the drop in level rather than a decline in trend (see Figure 4 (D)). Further analysis indicates that the change in slope post intervention is in fact significantly positive in Spain (data not shown). The same is also true of Italy (data not shown).

It should be noted that interpretation and extrapolation of these examples may be problematic because:

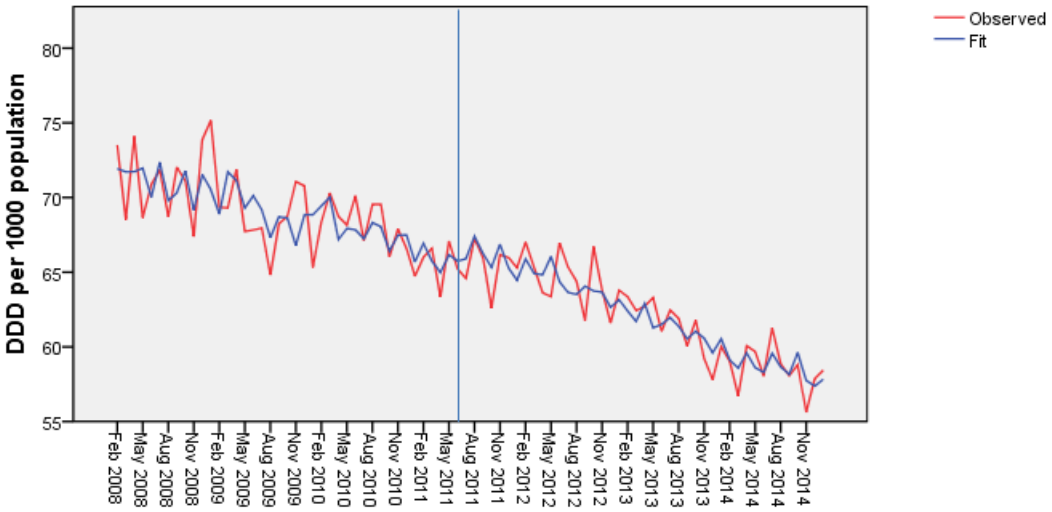
(1) Analysis of the impact of generic launch on volumes in high income countries with limited out of pocket payments may not reflect the situation in countries with different health or insurance systems;
(2) Other antibiotics in the same class had previously lost protection – in the case of meropenem, imipenem lost protection at a similar point in time in many of the countries and in the case of levofloxacin, ciprofloxacin lost protection several years before. Meropenen and levofloxacin do not therefore represent the first loss of protection within their respective classes. In short, sales prior to the loss of protection may include an effect of generic launch that cannot therefore be detected in these time series;
(3) the carbapenems are generally restricted in the hospital environment and will require microbiologist approval before use. The use of oral quinolones will also have been more restricted than perhaps other antibiotics that are used in both hospital and in the community; and,
(4) other changes in the environment, in policy or procurement practices may have influenced the post intervention slope or level. For example in England, antibiotic guidelines increasingly discouraged the use of quinolones (and cephalosporins) for fear of increasing the risk of *Clostridium difficile* infection.[8] Similarly we see a high degree of fluctuation in carabapenem volumes in two countries at or post intervention (Figures 4 (A) and 4(F)), the cause of which may well be unrelated to the launch of generic forms of meropenem.

Despite these caveats however it seems that no consistent impact of generic introduction can be detected using interrupted time series analysis.

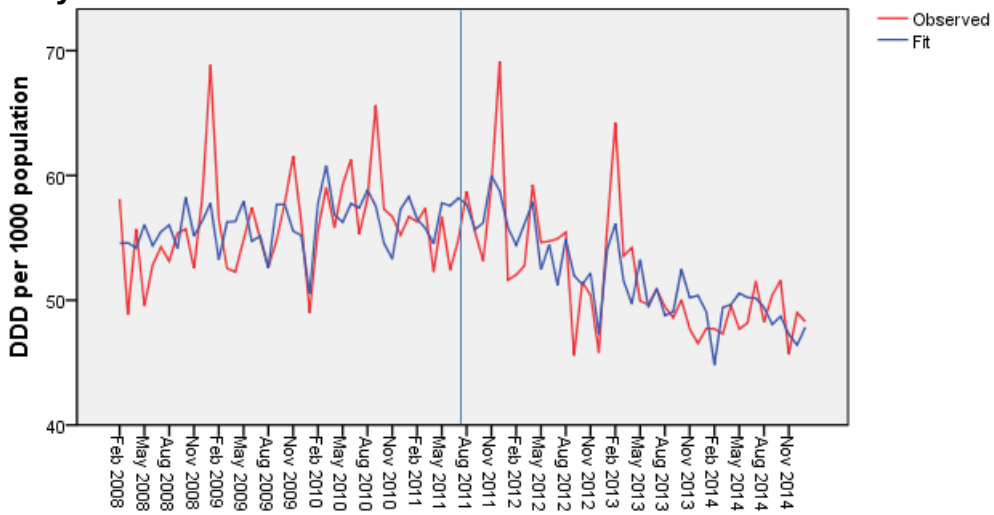
Figure 3: DDDs per 1000 population (seasonally adjusted) of oral quinolones – observed and fitted model

(Vertical line denotes month of first generic to levofloxacin)

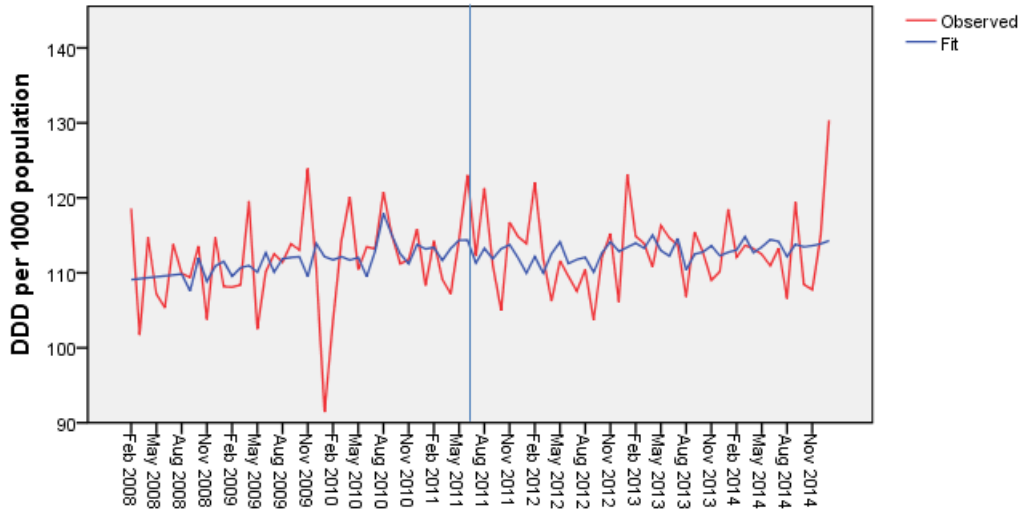
(A) France



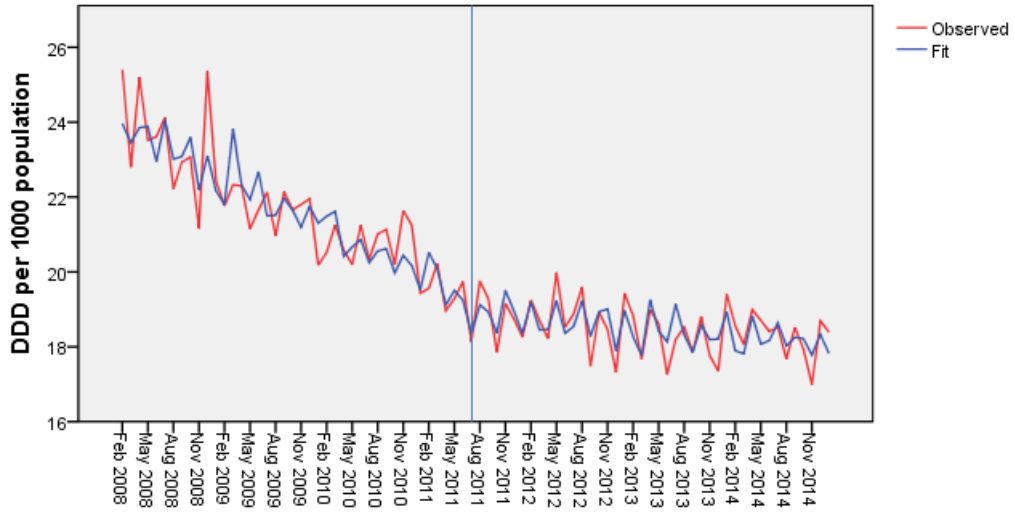
(B) Germany



(C) Italy



(D) UK


Observed
Fit
DDD per 1000 population
26
24
22
20
18
16
Feb 2008
May 2008
Aug 2008
Nov 2008
Feb 2009
May 2009
Aug 2009
Nov 2009
Feb 2010
May 2010
Aug 2010
Nov 2010
Feb 2011
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Feb 2012
May 2012
Aug 2012
Nov 2012
Feb 2013
May 2013
Aug 2013
Nov 2013
Feb 2014
May 2014
Aug 2014
Nov 2014

(E) USA


Observed
Fit
DDD per 1000 population
120
110
100
90
80
70
Feb 2008
May 2008
Aug 2008
Nov 2008
Feb 2009
May 2009
Aug 2009
Nov 2009
Feb 2010
May 2010
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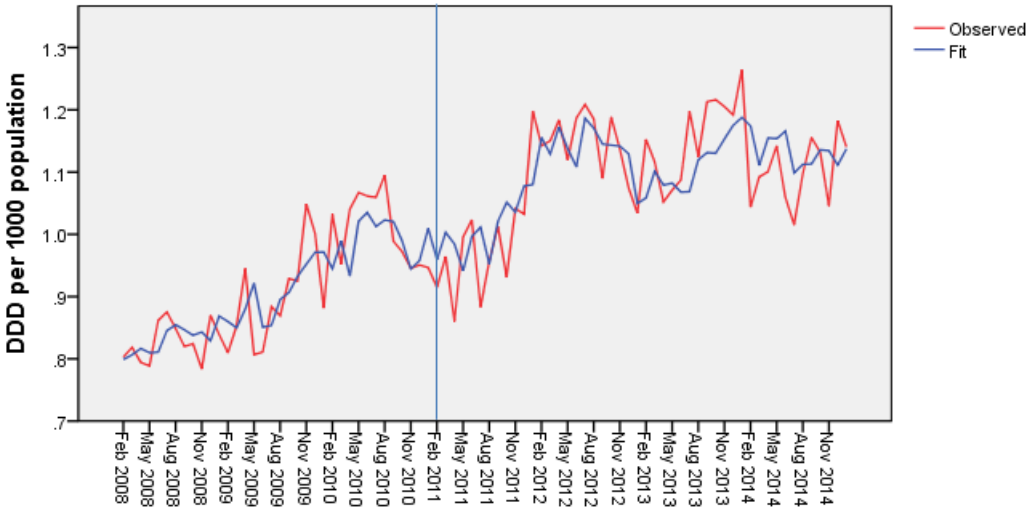
Nov 2014

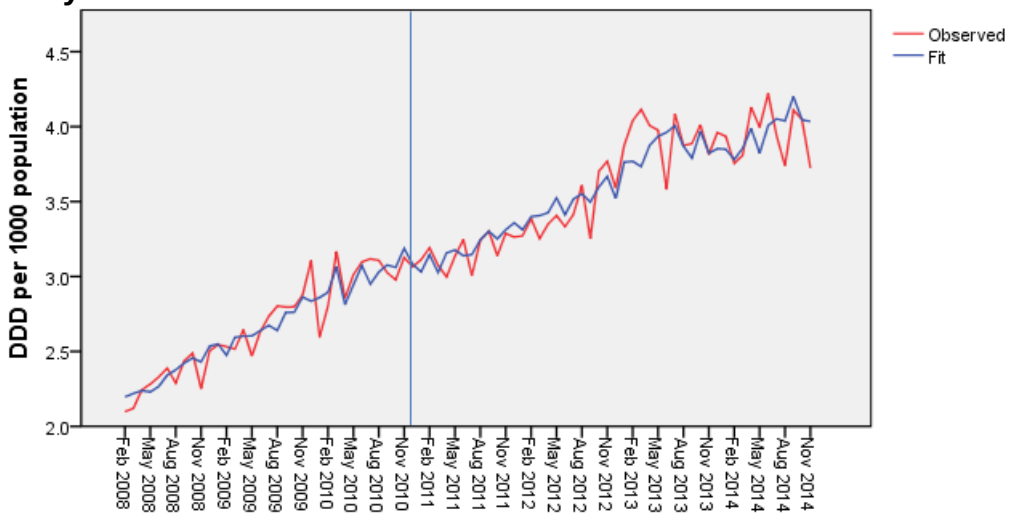
Figure 4: DDDs per 1000 population of carbapenems (seasonally adjusted) – observed and fitted model

(Vertical line denotes month of first generic to meropenem)

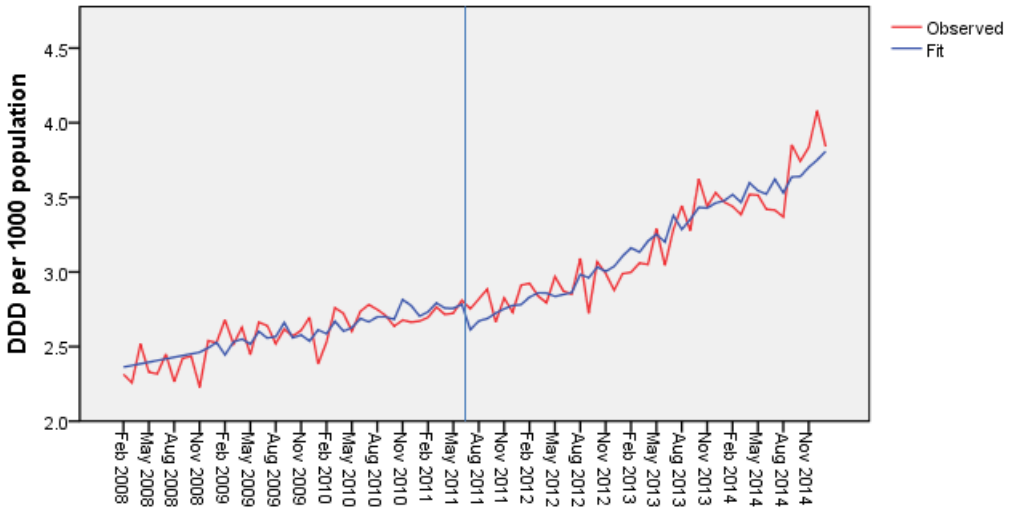
(A) France



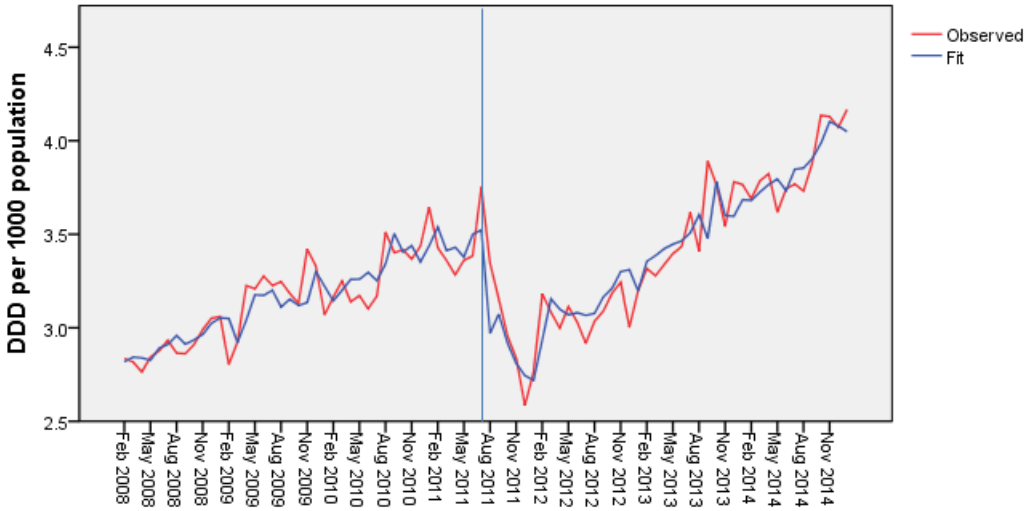
(B) Germany



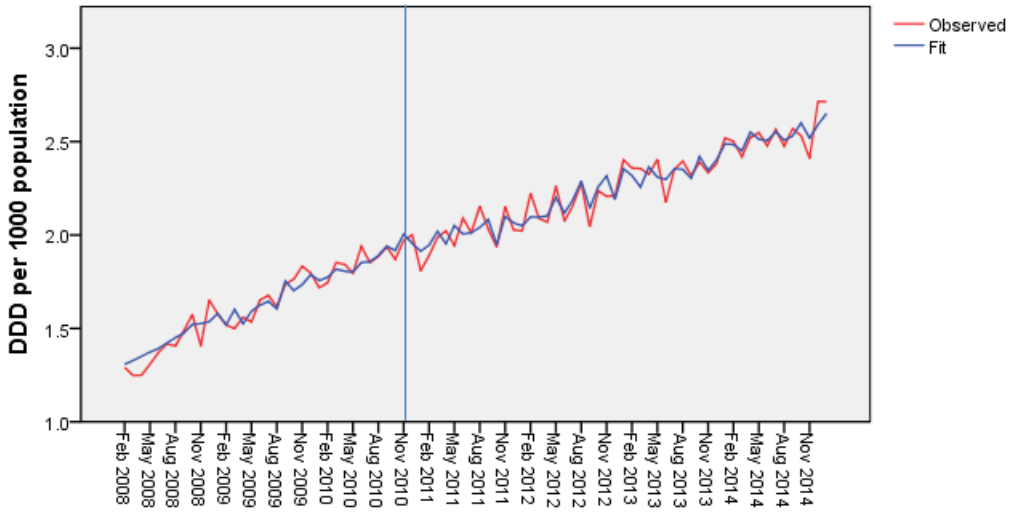
(C) Italy



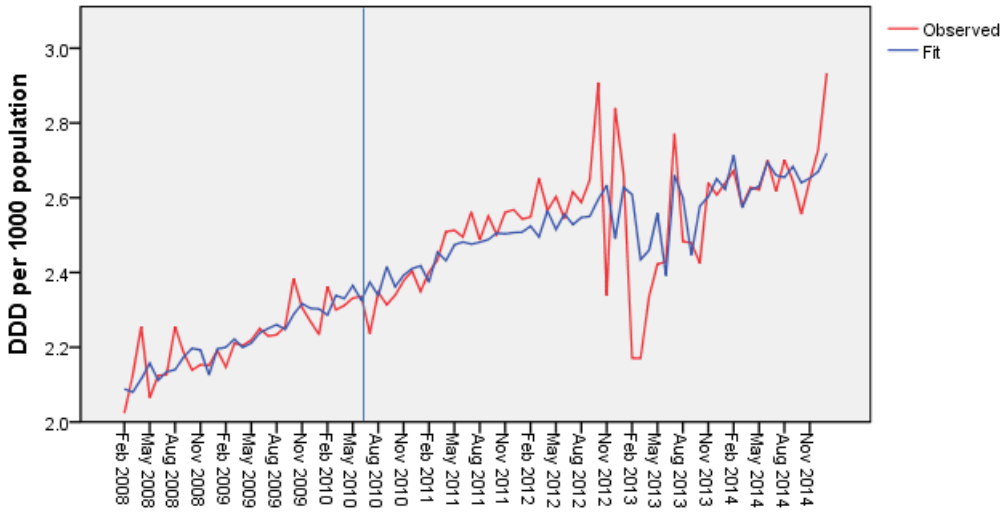
(D) Spain



(E) UK



(F) USA



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