A Review of Rise of Modern Pharmaceutical Biotechnology in Antibiotic Drug Discovery and Development and Future Implications

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Background

- **1928: Dawn of antibiotic era**
- **Impact of Antibiotics on global health**
  - Bacteria infectious disease burden reduced – pandemics, STIs, sepsis, etc.
  - Life expectancy more than doubled
- **Mid 1945-62** - most productive era
  - 20 new classes of antibiotics put into clinical use by way of Empirical R&D
  - Most antibiotics were from microbes
  - These are the antibiotics still sustaining the world today
- **1962-2000: R&D focused first on rational computer aided synthesis and then on genomic screening of available molecules**
  - **Discovery programs do not bear much -** No new classes of antibiotics discovered
  - Inadequate R&D funding from governments and pharmaceutical companies into antibiotic research

crisis arising from last two factors

  - empty pipelines BUT AMR to all antibiotics currently in clinical use

- **Post 2000: Modern Biotechnology era has brought hope**

Renewed interest in R&D from natural sources (microbes)

  - **Modern biotech tools**
  - Five new classes of antibiotics **2000-2012**
  - **Hope so long as funding improves**

Objectives of the Current Research

Aim: Review advances in antibiotic R&D

Specific

- Describe trends and R&D focus areas by era and outcomes
- Identify classes of antibiotics approved for clinical use to-date
- Identify the most important innovations and technologies could yield new antibiotics to avert the crisis on the horizon
- Explore modern Biotechnological approaches to antibiotic R&D

Methodology

Study design	Systematic review of literature
Search strategies	• Search terms: antibiotic, biotechnology, research, development, methods, production • Data bases: Science direct, PubMed, Medline and open sources
Sampling procedure	Only peer reviewed articles and books were included (1928-2017)
Outcome variables	Trends in antibiotic R&D
	Classes of antibiotics currently in clinical use
	Innovations / Technologies have contributed to antibiotic R&D
	Current areas of focus for Antibiotic R&D
Data Management and analysis	• Descriptive analysis using microsoft excel • Innovations/Technologies were ranked based on significance

Results

Trends and focus areas Antibiotic R&D 1928 - 2017

Year	**1940s**	**Mid 1940s-1972**	**1970s**	**1980**	**1990s**	**Post 2000**
Name of Era	Primordial age	Golden age	Pharmacological age	Combinatorial chemistry age	Genomic age	Renascence age
Focus areas of Antibiotic R&D	Empirical R&D	Empirical R&D - Natural sources - Synthesis - Semi-synthesis	- Rational drug use - Rediscovery of existing classes	Computer aided drug design	High thorough put screening of existing molecule	Renewed interest in Natural sources
Results	Clinical use of antibiotics starts	20 classes introduced to clinical practice	No new classes	No new classes	No new classes	New classes

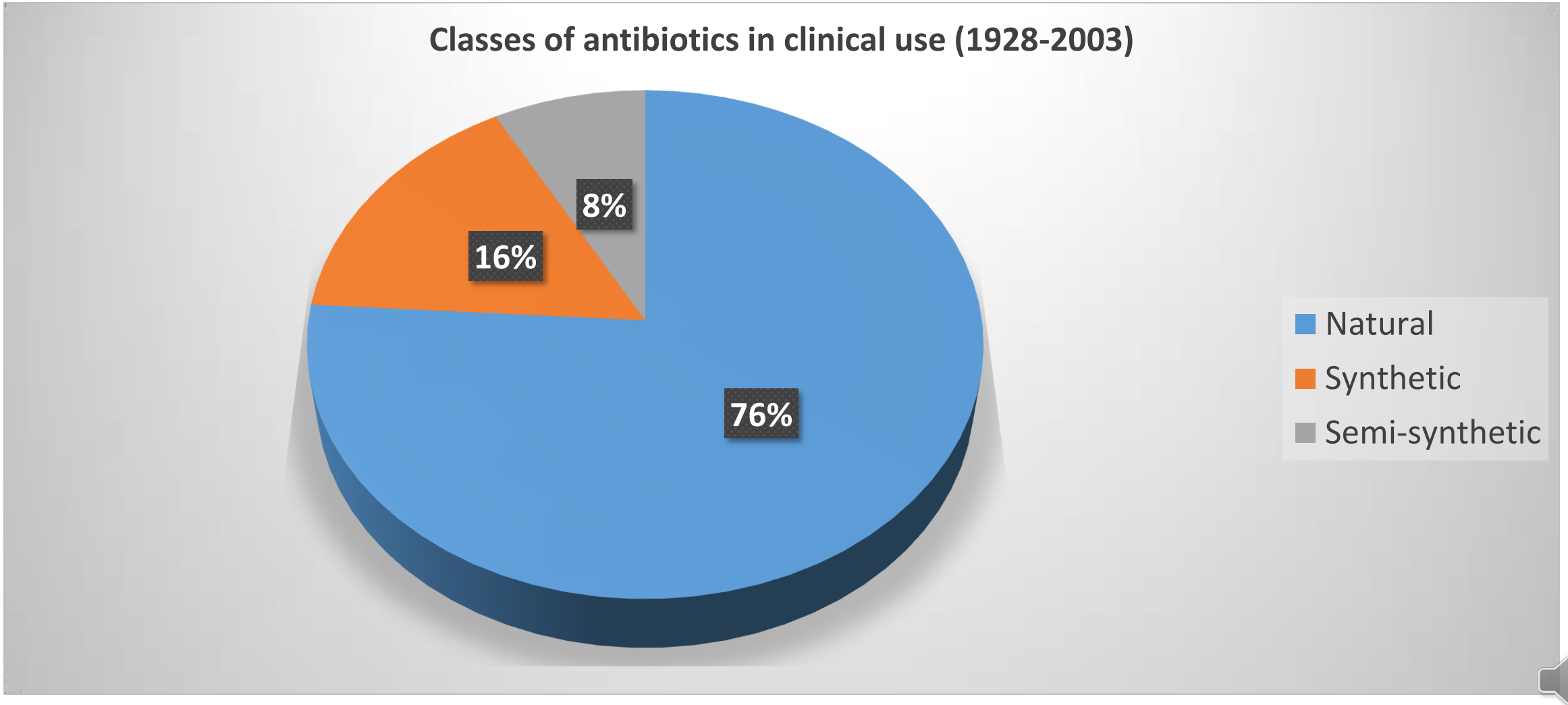
1962 — 2001

No New classes

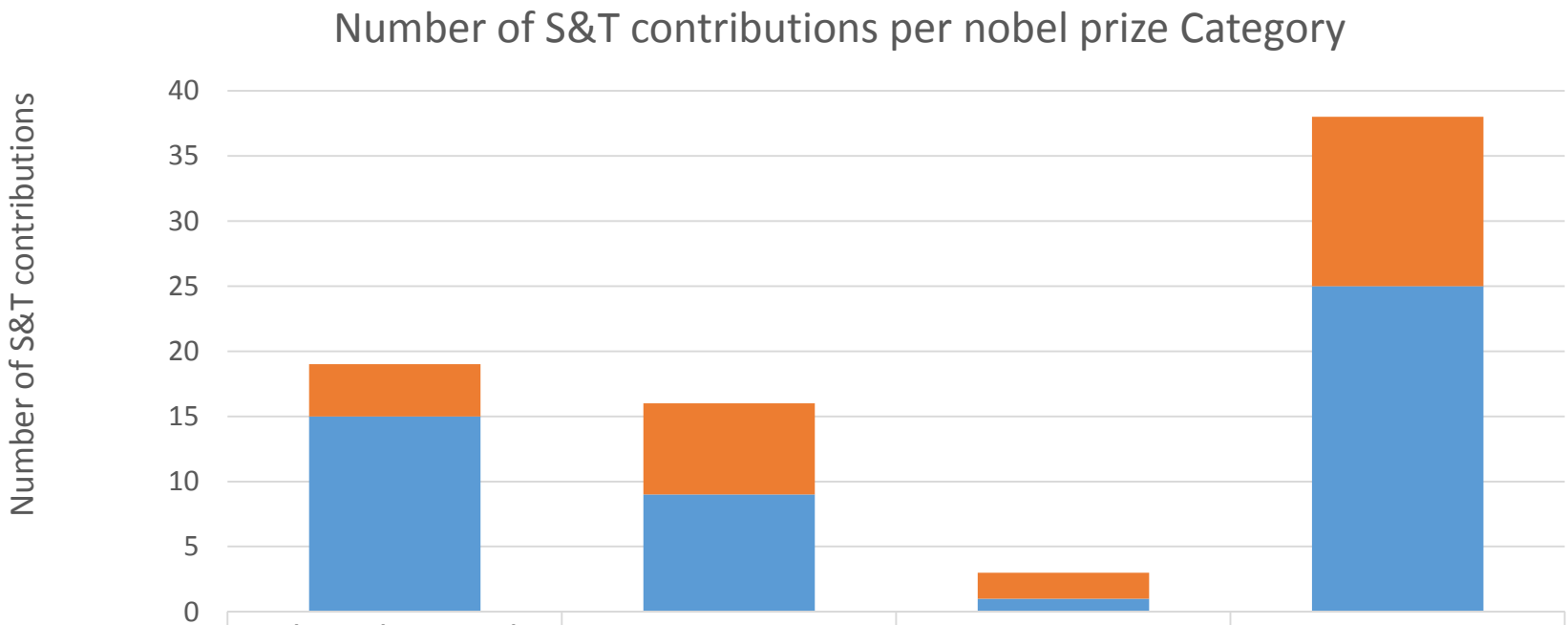
Table 1.1: Classes of Antibiotics Marketed from 1928 - 2012

No.	Class of antibiotic	Year of introduction	Source (Natural or Syntheic)	References
1	Sulfonamides	1935	Synthetic	
2	β-lactums (Penicillins)	1941	Natural	Oesterhelt, B. H., & Sass, p. (2010)
3	Aminoglycosides	1944	Natural	Oesterhelt, B. H., & Sass, p. (2010)
4	Cephalosporins	1945	Natural	Oesterhelt, B. H., & Sass, p. (2010)
5	Colistimethates (Polymixins)	1947	natural	Gurjar, M. (2015)
6	Nitrofurans	1947	Synthetic	Oesterhelt, B. H., & Sass, p. (2010)
7	Amphenicols (Chloramphenicol)	1949	natural	Oesterhelt, B. H., & Sass, p. (2010)
8	Tetracyclines	1950	Natural	Oesterhelt, B. H., & Sass, p. (2010)
9	Polypetide (Bacitracin)	1950	Natural	Frank, L. M., Johnson, B. (1947)
10	Hydrazides (Isoniazid)	1951	synthetic	Zumla, A., Nahid, P., & Cole S. T. (2013)
11	Macrolides	1952	Natural	Oesterhelt, B. H., & Sass, p. (2010)
12	streptogramines	1952	Natural	Oesterhelt, B. H., & Sass, p. (2010)
13	Amino coumarines (Novobiocine)	1956	Natural	Rutenburg, A. M., Shapiro, P., Schweinburg, F., Sylvester, E., Nakamura, M. (1956)
14	Glycopeptides	1956	Natural	Oesterhelt, B. H., & Sass, p. (2010)
15	Rifamycins	1957	Natural	Sensi, P. (1983)
16	Nitroimidazoles	1959	Semi-synthetic	Oesterhelt, B. H., & Sass, p. (2010)
17	Mycolic acid inhibitors (Ethambutol)	1961	Semi-synthetic	Zumla, A., Nahid, P., & Cole S. T. (2013)
18	Quinolones	1962	Natural	Oesterhelt, B. H., & Sass, p. (2010)
19	Lincosamides	1962	natural	Oesterhelt, B. H., & Sass, p. (2010)
20	Diaminopyrimidine (Trimethoprime)	1962	Synthetic	Eliopoulos, G. M., & Huovinen, P. (2001)
21	Oxazolidinones	2000	natural	Oesterhelt, B. H., & Sass, p. (2010)
22	Lipopeptides	2003	natural	Oesterhelt, B. H., & Sass, p. (2010)
23	Pleuromutilin	2007	natural	Renwick, M., Simpkins, V., & Mossialos, E. (2016)
24	Tiacumycin	2011	Natural	Renwick, M., Simpkins, V., & Mossialos, E. (2016)
25	Diarylquinoline	2012	Natural	Renwick, M., Simpkins, V., & Mossialos, E. (2016)

Classification of Antibiotics that are Currently in Clinical use According to Source



Novel prize Innovations/Technologies by categories, that had significant impact on Antibiotic R&D from 1928 – 2017

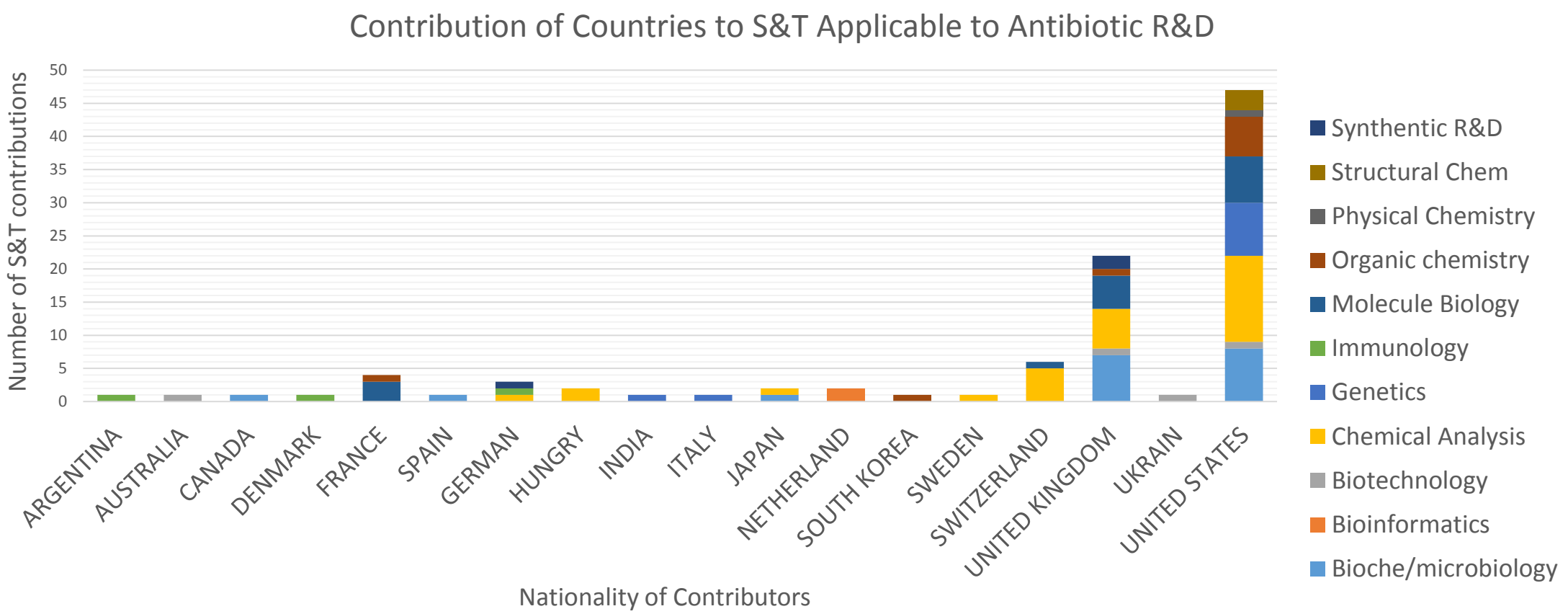


	Physiology and Medicine	Chemistry	Physics	Total
Second Line Contributions to Antibiotic R&D	4	7	2	13
First Line Contributions to Antibiotic R&D	15	9	1	25

Table 1.2: Innovations in S&T from 1928 – 2017 by Nationality and by Specific Field

Field of S&T	Nationality of S&T contributors																	**Total**
	ARG	AUS	CAN	DEN	FR	ESP	GER	HUN	IND	ITA	JAP	NET	RSK	SWE	SWI	UK	UKR	US	
Bioche/micr	-	-	1	-	-	1	-	-	-	-	1	-	-	-	-	7	-	8	**18**
Bioinform.	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	**2**
Biotech.	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	**4**
Chem. Anal.	-	-	-	-	-	-	1	2	-	-	1	-	-	1	5	6	-	13	**29**
Genetics.	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	8	**10**
Immunology	1	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	**3**
Mol. Biol.	-	-	-	-	3	-	-	-	-	-	-	-	-	-	1	5	-	7	**16**
Org. chem.	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	1	-	6	**9**
Phys. Chem.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	**1**
Str. Chem.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	**3**
Synth. R&D	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	2	-	-	**3**
Total	**1**	**1**	**1**	**1**	**4**	**1**	**3**	**2**	**1**	**1**	**2**	**2**	**1**	**1**	**6**	**22**	**1**	**47**	**98**

Graphical Presentation of Innovations in S&T from 1928 – 2017 by Nationality and by Specific Field



Pie Chart Presentation of Innovations in S&T from 1928 – 2017 by Nationality of contributors

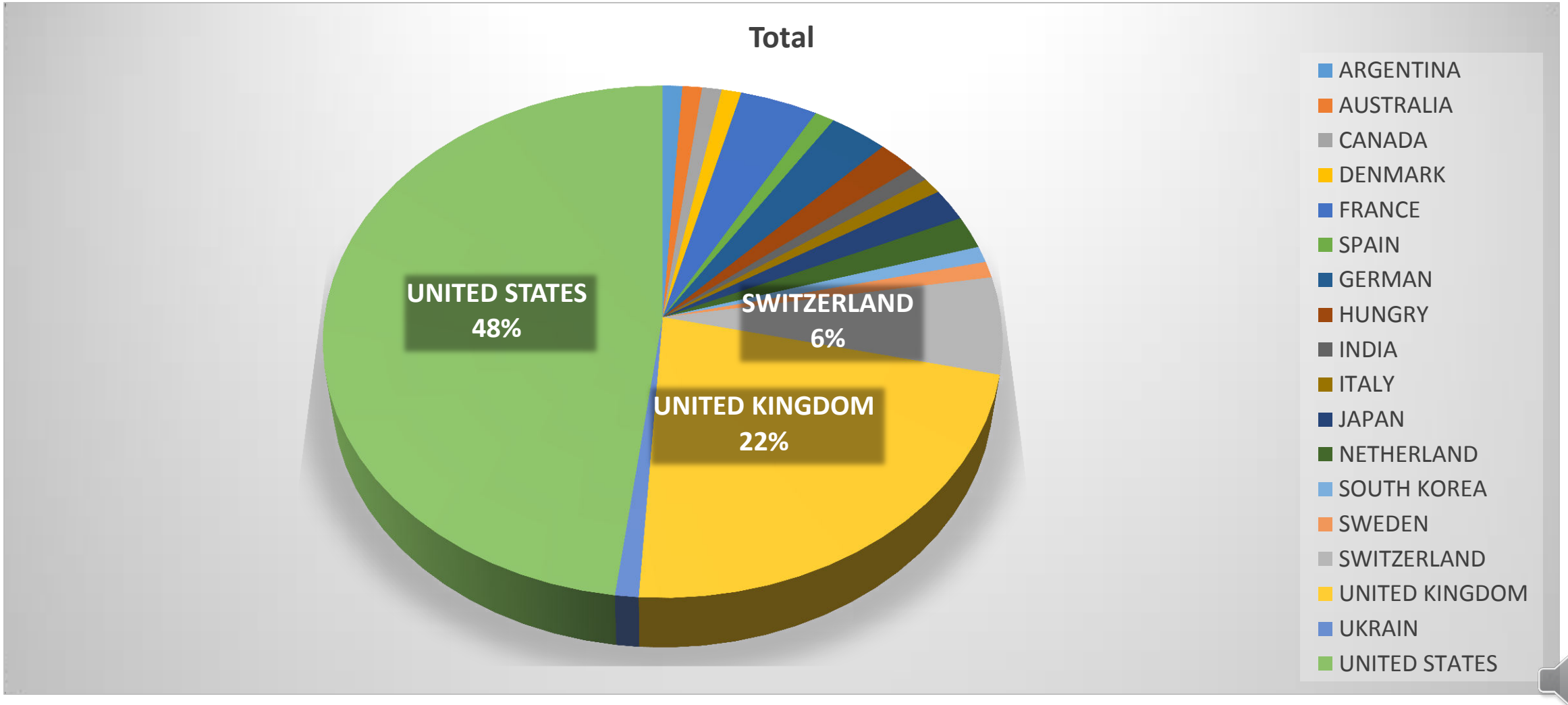
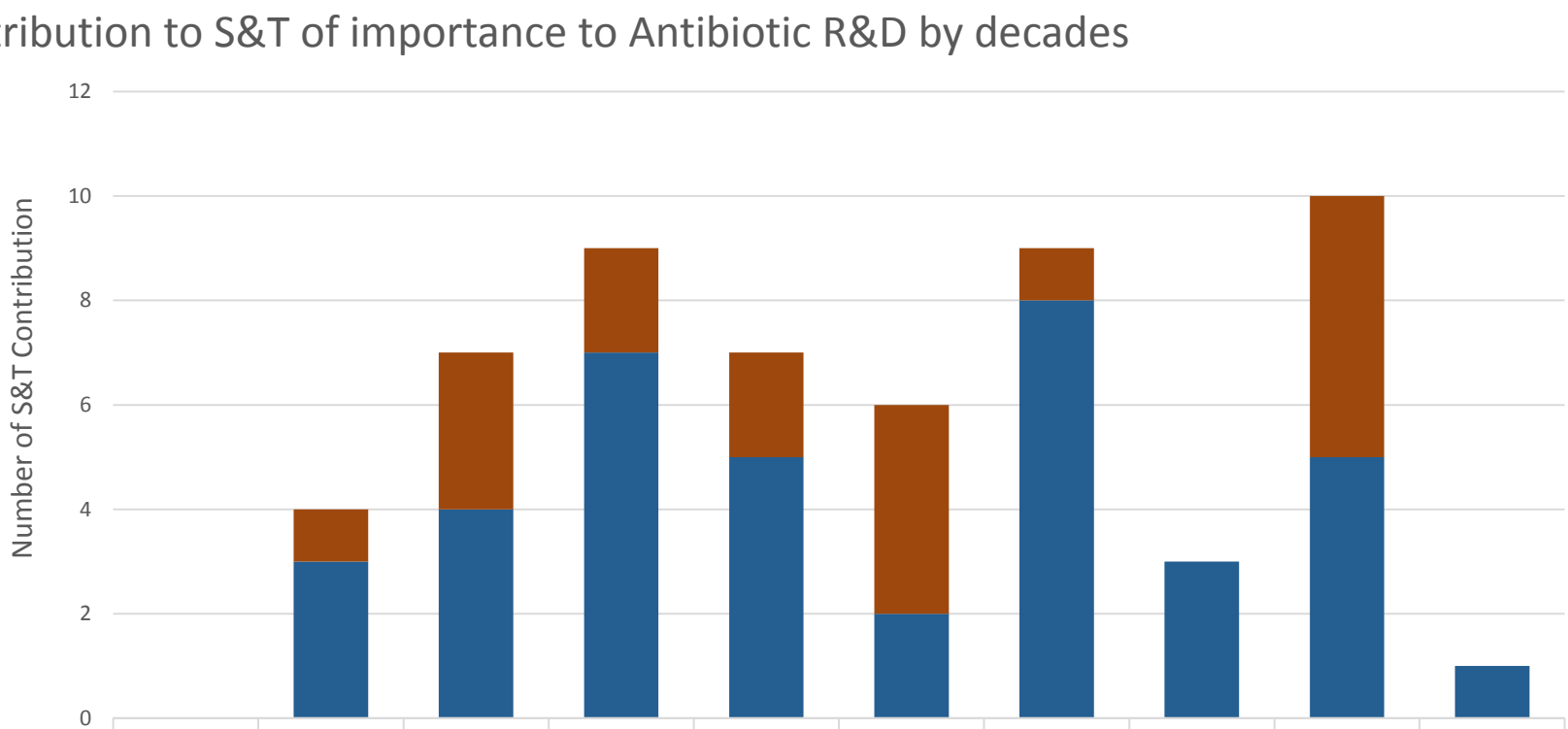


Table 1.3: Contributions to S&T of importance to antibiotic R&D according to decades

Type of contribution		Category	1928-39	1940-49	1950-59	1960-69	1970-79	1980-89	1990-99	2000-10	2010-17	Total
Contributions that won Nobel prizes	First line contributions	Phys or Med	2	2	4	3	1	-	1	2	-	15
		Chemistry	-	1	1	2	-	3	2	-	-	9
		Physics	1	-	-	-	-	-	-	-	-	1
	Second line contribution	Phys or Med	-	-	-	-	1	2	-	1	-	4
		Chemistry	-	1	2	-	-	1	-	2	1	7
		Physics	-	-	-	-	-	2	-	-	-	2
	Subtotal		3	4	7	5	2	8	3	5	1	38
Significant contributions but no Nobel awards			1	3	2	2	4	1	-	5	-	18
Total			4	7	9	7	6	9	3	10	1	56

Graphical Presentation of Contributions to S&T of importance to Antibiotic R&D according to decades



Category	1928-39	1940-49	1950-59	1960-69	1970-79	1980-89	1990-99	2000-10	2010-17
Significant contributions but no Nobel awards	1	3	2	2	4	1	0	5	0
Contributions that won Nobel prizes	3	4	7	5	2	8	3	5	1

Modern Biotechnological Approaches to Antibiotic R&D

1. Rescuing and Repositioning older antibiotics and other drugs using siRNA genome wide screens

Table 1.6: List of Repositioned Drugs for Antibacterial use currently in Different Stages of Clinical Trials

Drug	Original Indication	New Indication	Clinical Trial stage	Reference
PNU-100480	MRSA	Tuberculosis	Phase I	Perwitasari, O., Bakre, A., Tompkins, M. S., Tripp, R. A., (2013)
Sulphamethoxazole-Trimethoprim	Generic antibacterial	Tuberculosis	Clinical use	
Raloxifen	Osteoporosis + Brest cancer	P. Aerogenosa	Pre-clinical	

Modern Biotechnological Approaches to Antibiotic R&D

2. Natural sources based on advanced Technology combined with synthetic modification

- 99 % are unculturable and not yet explored
- The OSMAC approach
- Unexplored environments e.g. marine, soils
- Non multiplying microbes

Conclusion and Recommendation

- Antibiotic R&D is inherently a difficult undertaking
- Modern Biotechnology has proved to be useful in antibiotic R&D
- Without adequate funding of antibiotic R&D, a serious crisis looms on the horizon
- Centers of excellence in antibiotic R&D in places like Africa